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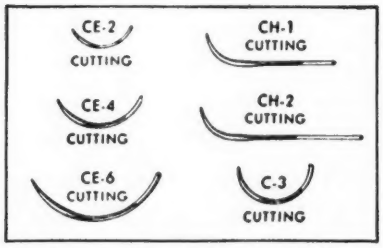

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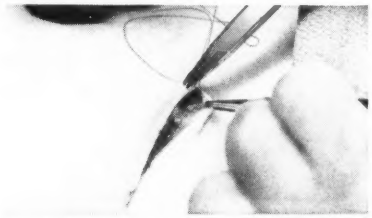

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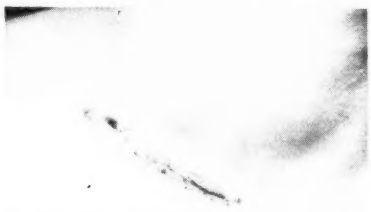

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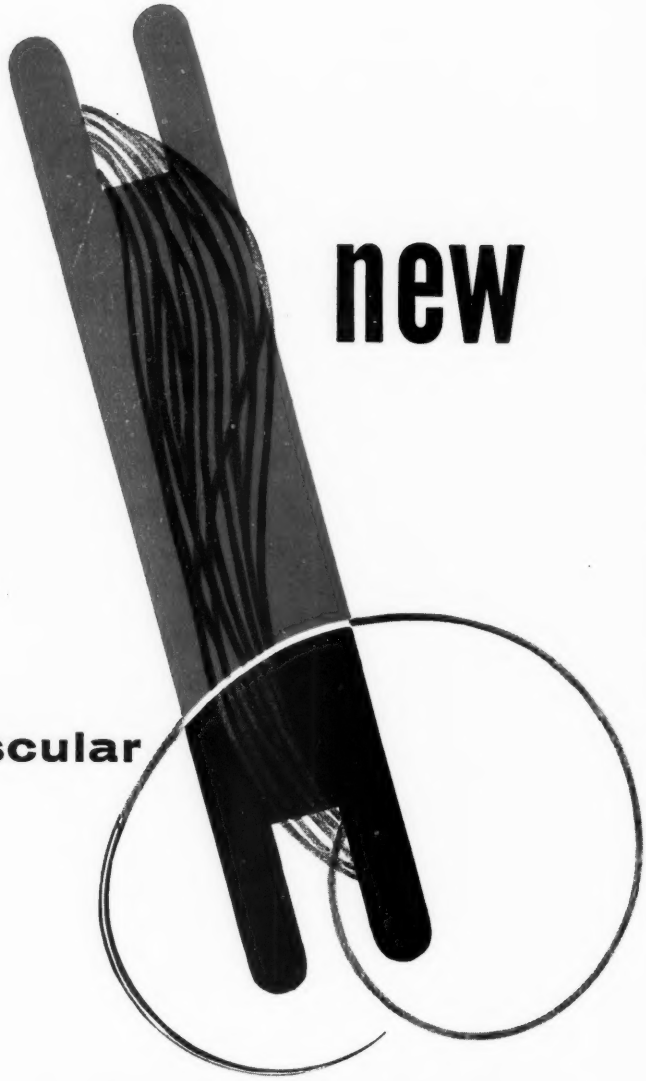

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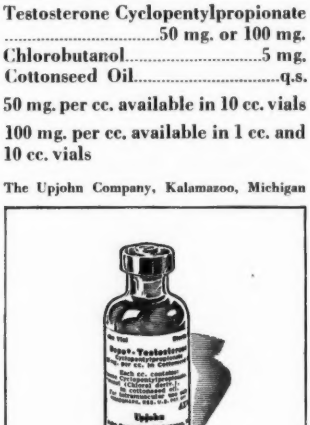

SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 99 JULY, 1954 NUMBER 1

OBSERVATIONS ON ADRENOCORTICAL FUNCTION IN PATIENTS UNDERGOING OPERATIONS UPON THE BONES AND JOINTS

JAMES A. NICHOLAS, M.D., PHILIP D. WILSON, M.D., F.A.C.S., and CHARLES J. UMBERGER, Ph.D., New York, New York

PREVIOUS study by the authors of 125 patients subjected to injury and operation upon the bones and joints revealed several patterns of stress response as determined by serial preoperative, postoperative, and convalescent eosinophile counts and other tests (4). Among the interesting observations was the fact that the vast majority of eosinophile counts were on the upswing by the third postoperative day. However, levels which persisted below 50 per cent of the preoperative level at the fifth day suggested complications. Moreover, the use of plastic and large metallic fixative appliances, except in cases of fresh fractures, tended to produce relative postoperative eosinopenia for 30 to 40 days in some cases, when compared with other cases in which such implants were not used. The need for further, more exhaustive study of such phenomena prompted the subsequent work described in this report. The ultimate aim is to study the relation of prolonged stress to the healing of bone.

METHOD OF STUDY

Patients who undergo operations upon the bones and joints offer favorable material for metabolic study, particularly because extrarenal losses of fluid are inconsiderable. Measurement of dietary and fluid intake and quantitative determination of urinary nitrogen and electrolyte excretion yield accurate information concerning significant changes that may be taking place in the body. We have employed these methods and also the measurement of the 24 hour urinary excretion of neutral 17-ketosteroids in a number of cases. We wish to present the results observed in 8 patients together with conclusions drawn from their study. All patients had preoperative levels obtained as a control. For 5 consecutive days after operation and also periodically during convalescence, identical studies were repeated. All patients had serial eosinophile counts and were carefully observed with regard to temperature, urinary excretion, and other vital signs. Finally, the dietary intake was charted from weighed samples.

Eight patients were studied in this manner. Four were classified as cases for lesser surgery because they required neither blood transfusion nor more than 2 hours of anesthetic time. They were young girls in their early teens undergoing elective procedure for long-standing orthopedic disabilities. Four patients were classified as cases for major surgery because they required more than 2 hours of

From the Hospital for Special Surgery, New York, N. Y.
This paper is based upon work that is being done under a grant from the Association for the Aid of Crippled Children, New York, N. Y.

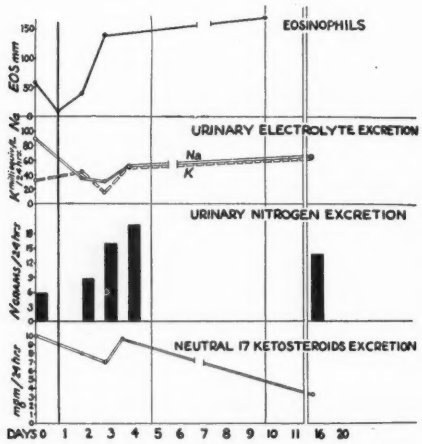

Fig. 1. Surgery of lesser severity. Case 6, D.O., female, aged 13 years, slipped capital femoral epiphysis, Smith-Petersen nailing.

anesthesia and were transfused during the operation. All 4 of these patients were in pain preoperatively and had been chronically ill with long-standing ankylosing arthritis of the hips. Three of these patients undergoing major surgery were on cortisone at some time during their convalescence. The fourth patient had a severe wound complication postoperatively. It can be seen, therefore, that the cases can be broken down into those patients with severe surgical stress imposed upon

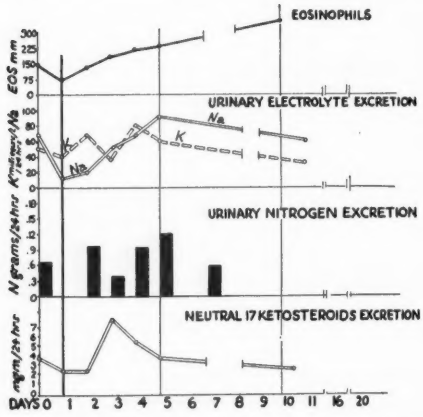

Fig. 2. Surgery of lesser severity. Case 4, M.A., female, aged 13 years, Still's disease, supracondylar osteotomy.

antecedent chronic illness, and those who were exposed to moderate or less severe surgical stress. The data presented in this paper are from 2 cases of each group.

RESULTS

All of the patients responded to the operations with a varying amount of decrease in vitality, urinary output, fluid intake, and caloric intake. During this time, eosinopenia was pronounced. As the vital functions tended to return to normal, the eosinophile levels rose. Without exception, when comparing the two groups, the more severe the surgery, the more profound was the metabolic response to it, regardless of the preoperative condition of the patient.

URINARY 24 HOUR NITROGEN EXCRETION

In 6 of the cases, the urinary 24 hour nitrogen excretion was elevated considerably postoperatively even while caloric intake was very low. In the 2 cases in which there was a fall in the immediate urinary nitrogen excretion, there was a sharp rise after 4 days. One of these 2 patients was given 100 milligrams of cortisone daily beginning 24 hours postoperatively. In the second there also occurred a delayed rise in urinary 24 hour nitrogen excretion, but this was associated with a marked renal retention lasting for 3 days postoperatively. The operation was a transfer of the patellar tendon and it was performed with a tourniquet. It was thought that the disturbance of kidney function might have been due to the use of this. In all 4 cases represented in Figures 1, 2, 3, and 4, urinary nitrogen excretion was considerably increased in the immediate postoperative period. It is interesting that this reaction occurred even while caloric intake was decreased.

ELECTROLYTE EXCRETION

The responses of sodium and potassium to stress were marked. While plasma potassium levels usually dropped slightly during the first 24 hours postoperatively, the urinary potassium excretion rose during the first 24 hours and tended to return to normal by the third or fourth postoperative day. In all the cases studied, plasma sodium levels fell for several

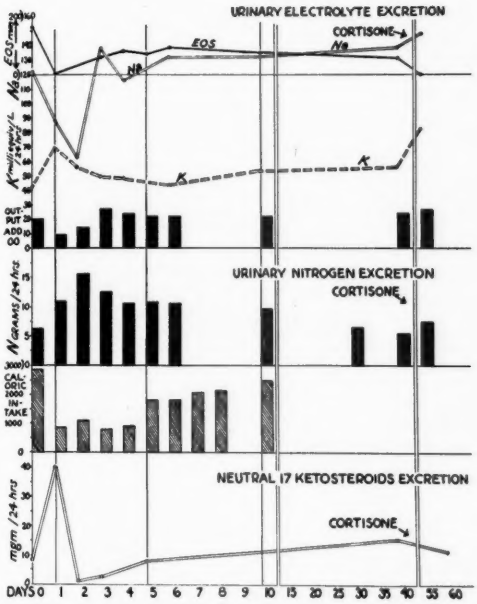

Fig. 3. A case of major surgical severity with marked stress response. M.W., male, aged 30 years, acrylic replacement of left hip.

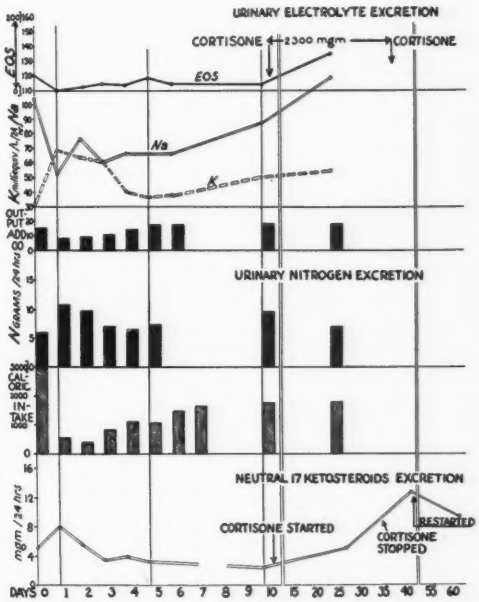

Fig. 4. A case of major surgical severity with no postoperative complication. B.E., female, aged 28 years, vitallium arthroplasty of left hip for rheumatoid arthritis.

days, while urinary excretion of sodium was also low during this time. Thereafter, with diuresis, sodium excretion rose rapidly. Marked sodium retention and potassium loss were especially evident in surgery of greater severity.

17-KETOSTEROID EXCRETION

The response to operation in the excretion of neutral 17-ketosteroids varied. In surgery of lesser severity, the urinary 17-ketosteroid level did not rise significantly in any case, except in Case 4 (Fig. 2). Here a small rise occurred 48 to 72 hours postoperatively and lasted only 1 day. On the other hand, in surgery of greater severity, the urinary 17-ketosteroid level rose in 2 cases within 24 hours and in 1 case within 48 hours. In the fourth case, however, the level dropped sharply. This occurred in the patient noted previously who had been on cortisone from 24 hours postoperatively. A sustained postoperative rise in the 17-ketosteroid excretion was seen in only 1 of the cases, and that occurred in the patient who had the wound complication postoperatively. Thus, while eosinophile changes and urinary electrolyte changes were characteristic following surgery, the 17-ketosteroid excretion varied depending upon the degree of surgery and apparent peculiarities of response of the patient clinically. In Figures 3 and 4 notice the short duration of the rise in 17-ketosteroid excretion. In 3 of the 8 patients studied no postoperative elevation of the 17-ketosteroids was found at any time.

DISCUSSION

From the study of electrolyte changes and changes in the eosinophile count, it has been demonstrated by many observers, including Selye, Browne, and Moore, that following surgery or injury, adrenocortical stimulation occurs for 2 to 4 days, followed by a withdrawal phase of the corticoid substances. Most studies utilize the urinary 17-ketosteroid examination as an index of adrenocortical stimulation along with these other

tests, but observers such as Hardy, and Thorn and associates have pointed out that postoperative 17-ketosteroid values did not change reliably or serve as an indicator of adrenal stimulation as well as other tests. To date, this has been thought to be due to a variation in response from patient to patient depending upon the degree of previous depletion. Yet some patients show profound, sustained elevation in urinary 17-ketosteroids, while others show sharp, transient rises, and still others show fall in excretion. While maximal corticoid effects occur apparently for 3 to 4 days after operations on the bones and joints, ketosteroids often do not mirror this increased adrenocortical activity. In the 4 cases illustrated here, the level of the 17-ketosteroid excretion did not show any prolonged postoperative rise during the time in which eosinophile counts were depressed, and while there was increased potassium excretion along with sodium retention and increased nitrogen excretion. It can be seen that, in the cases of surgery of greater severity, for example, only a 24 hour period of peak 17-ketosteroid excretion was noted, and then levels dropped sharply to or below the preoperative figures; and yet one can readily see that changes paralleling this fall of cortical activity in the eosinophile count and the electrolyte studies lagged between 24 and 72 hours. In other words, in the so-called "corticoid withdrawal" phase, during which the patient begins to recover his vitality and his balances turn toward normal, falling 17-ketosteroid excretion was not noted. However, in cases of lesser severity, the 17-ketosteroid level did not depict any increased adrenocortical activity at all, although there was postoperative eosinopenia. This leads to only one conclusion. Either 17-ketosteroid excretion as a measure of postoperative stress is not a sensitive indicator, because the changes are transient and depend largely upon the degree of intensity of stress, or the test is not an accurate index of actual increased adrenocortical androgenic steroid activity.

Because of this discrepancy, further studies were indicated. Further work has shown that previous data on neutral 17-ketosteroid excretion as an expression of increased adrenocortical activity may be inaccurate for reasons inherent in the chemical tests involved in the 17-ketosteroid determination. In a subsequent report it will be shown by ultraviolet and infrared spectrophotometric studies that there are other fractions in the steroid analysis which appear to mirror more closely some of the changes seen in the patient clinically and in the chemical studies during convalescence. Even here, one must keep an open mind as to whether 17-ketosteroid activity actually mirrors adrenal function or is the effect of many other organs acting as well.

CONCLUSIONS

The usual responses in a patient subjected to operative procedures on the bones and joints are observed as follows:

1. Eosinopenia lasts a varying length of time accompanied by sustained potassium urinary loss, increased nitrogen 24 hour excretion, and sodium retention.

2. The 17-ketosteroid level, however, does not constantly mirror this evidence of increased adrenocortical function postoperatively.

3. The present methods of measuring 17-ketosteroid excretion require further study before accepting the results as an index of adrenocortical function.

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THE PROCESS OF ANOXIC DEATH IN NEWBORN PUPS

H. G. SWANN, Ph.D., J. J. CHRISTIAN, M.D., and C. HAMILTON, M.D., Galveston, Texas

THE processes of death and resuscitation have recently been described for adults in considerable detail (3, 4). We have knowledge of the points of circulatory and respiratory failure at which reversal of the death process may still be accomplished. The process of anoxic decerebration is also known, along with the boundaries of reversible and irreversible cerebral insult. From this knowledge about adult dogs, some limiting estimates may be made about the behavior of man in similar circumstances.

In the case of the fetus and the newborn, their reactions to anoxia with respect to heart rate and breathing rate are also known, but simultaneous measurements of the two physiologic variables during the death process are lacking, just as was the case for the adult until recently. The changes in blood pressure are also unknown. These reactions are of interest because the commonness of asphyxia neonatorum still poses a major medical problem. Hence, the process of anoxic death in the newborn has been investigated, particularly with respect to the interrelation of respiratory and cardiovascular behavior. Newborn pups were used for investigation, their state of maturity when born being roughly comparable to that of the newborn infant. Their cardiovascular and respiratory behavior was ascertained, and as well, the changes in blood gases and blood acidity during the death process. The point of circulatory failure was ascertained in a preliminary way.

METHODS

Pups aged 3 or 4 days were used in all experiments. At this time their resistance to anoxia is, as in most newborn mammals, very great. The pups were made anoxic by running a stream of pure nitrogen through a simple mask placed over their heads, avoiding any other interference with the pup's breathing. The mask was a tube 9 centimeters long and 4.5 centimeters in diameter. A sheet-rubber membrane, with a hole cut in its center, was placed on one end. The pup's head was thrust through the hole, and the membrane left to fit snugly around the animal's neck. A rubber stopper was placed in the other end of the tube through which the nitrogen was blown. The membrane around the pup's neck was deliberately bled of nitrogen, and thus a stream of nitrogen was left to flow by the pup's nose and mouth. Nitrogen of high purity (99.99 per cent) was used.

The pup's respiratory rates were recorded by direct observation or in some cases by recording the pressure fluctuations inside the head mask. The blood pressure was recorded optically with an isometric Bourdon-tube manometer, the carotid artery being cannulated for this purpose with a 22 gauge syringe needle. Because the pups stayed alive for a long time with very low blood pressures and because detection of less than a millimeter of mercury of pressure was found to be necessary, a very sensitive recording manometer was used. This sensitivity, however, reduced the rapidity of response of the system. The figures, therefore, which will be presented for the systolic pressure are perhaps somewhat low. In many of the pups, serial electrocardiograms were also taken during the course of anoxia; lead II was employed, with subcutaneous needle electrodes.

In 9 pups, the changes in arterial blood gases and hydrogen ion concentration were also observed in serial fashion. Because approximately 5 milliliters of blood were drawn in each sample, or approximately one-quarter of the pup's blood, it was thought advisable to make no more than one blood analysis on each pup. The data to be presented on the blood gas changes, therefore, represent the single sample drawn from 1 pup's carotid artery. Each point in the series data was given by a different pup. The whole blood was analyzed for oxygen and carbon dioxide by the method of Van Slyke and Neill. The

From the Department of Physiology, University of Texas Medical School, Galveston.

TABLE I.—ANOXIA IN NEWBORN PUPS

Time after start, mins.	Whole blood: O_2, vols. per cent	CO_2, vols. per cent	CO_2 tension, mm. Hg	$BHCO_3$, mM./L.	p_H	Respiratory rate, per min.	Blood pressure, mm. Hg	Heart rate, per min.
						Averages		
0	17.4	48.4	46	24	7.34	30	80/75	230
1						5	39/23	240
2						5	28/21	80
3						3	43/28	75
4						2	56/65	65
6	0.3	37.9	54	17	7.12	4	56/42	70
10	0.4	33.6	84	15	6.84	2	23/18	45
12	0.5	31.8	65	14	6.95	1	20/11	45
15	0.3	20.4	42	9	6.96	1	20/10	45
17	0.4	22.2	85	9	6.62	½	15/10	45
20						½	11/8	35
24	0.5	41.9	160	17	6.62		7/6	31
28	0.3	30.0	157	12	6.43		6/5	28
30	0.9	39.6	208	14	6.43		5/4	6

hydrogen ion concentration was measured with a glass electrode at room temperature, and the observed readings corrected to a temperature of 38 degrees. In computing the carbon dioxide tensions and the blood bicarbonate, the methods of Van Slyke and Sendroy were used.

With the exception of pup No. 1 of Table II, in which ether anesthesia was employed, no anesthetic was used in the experiments. The anoxia itself served to render the pup unconscious for the exposure and cannulation of the carotid artery.

RESULTS

In Table I are shown the changes in blood gases, hydrogen ion concentration, breathing, blood pressure, and heart rate during the process of death. The chemical analyses were made as discussed previously on a different pup at each point. The blood samples drawn at 24, 28, and 30 minutes were drawn from the left heart directly, for these pups were essentially dead. The circulatory and breathing changes shown in the last three columns of the table are averages of several pups, in none of which were blood samples taken.

The table shows that the arterial blood oxygen fell to the vanishing point by 6 minutes. The carbon dioxide content declined for some 20 minutes and then rose again in the postmortem samples. The carbon dioxide tension rose slowly, finally reaching very high levels, and the hydrogen ion fell to 6.6 or even (postmortem) 6.4. The acidosis is evidently extreme.

Respiratory rates fell rapidly over the first minute of exposure to one-sixth the normal rate. They then slowly declined over the next 20 minutes, rates being, just before the last gasp was taken, 1 breath per 2 or 3 minutes. The time of the last breath varied considerably, the extremes ranging, in the 14 anoxic pups observed, from 11 to 19 minutes. Heart rates fell rapidly during the induction of anoxia and then slowly declined still more. The bradycardia is not accompanied with a dropping out of the P wave in the electrocardiogram, as is true of the adult. Electrical activity from the heart ceased, in the 5 pups in which it was measured, at 23, 25, 30, 48, and 54 minutes, respectively. The blood pressure slowly declined until at 20 minutes it averaged 11/8. Considerable individual variation was also observed, as brought out in Table II. The time of disappearance of the last carotid pulse varied from 16 to 29 minutes, according to the data taken from a group of 14 dogs.

That these very low blood pressures still cause circulation is shown in the data in Table II. In this experiment, resuscitation was attempted: the pups were tracheotomized after 17 to 32 minutes of anoxia, and then their lungs were insufflated with oxygen at a rate of about once per second. When blood pressure and breathing were restored, the animals were sacrificed. The experiment reported was done in order to find out when, approximately, circulation ceases in these animals, circulatory failure being defined, in this context, as that accompanying a blood pressure so low that it can no longer bring reoxygenated blood out of the lungs and thus effect resuscitation. Table II shows that blood pressures of the order of about 8/6 are still adequate in these newborn pups to circulate reoxygenated blood and induce resuscitation, that the pups can readily be resuscitated after they have ceased breath-

ing for some minutes, and that some may be resuscitated (e.g. No. 8) after even 26 minutes of anoxia and with a blood pressure of about 5/4. As will be discussed later, their reactions are in sharp contrast to those of adult dogs.

DISCUSSION

The pronounced cardiac slowing in response to anoxia was examined closely, in the newborn and in fetuses, by Bauer (1, 2). It is probably not mediated by the vagus nerves, as is true for the bradycardia of anoxia in the adult, for the cardioinhibitory afferent fibers do not mature until later in life. The presence of the P wave in the electrocardiogram of the pups is further proof of this fact, since in the adult the reaction is vagus-mediated, with a disappearance of the P wave. The advantage of this bradycardia is evident: the slowly beating heart consumes far less oxygen and other metabolites, thus permitting it to continue functioning through much longer periods of anoxia. Such episodes are probably not uncommon, not only during parturition, but also during the whole course of intrauterine life.

The observed fall in blood pressure accompanying the bradycardia is no doubt a reflection of a decreased cardiac output. By 10 minutes, the blood pressure had fallen to about 23/18; that this is an effective circulating pressure is shown by the fact that the pups may readily be revived at this point. Now in adults, the point of circulatory failure is at a systolic blood pressure, during the process of death, of 100 millimeters of mercury. But in the pups, pressures far lower than this are still effective. As Table II shows, if the systolic blood pressure exceeded 8 millimeters of mercury, all pups were successfully resuscitated; the comparable figure for diastolic pressure is 6 millimeters of mercury. Evidently, then, a blood pressure of 8/6 still continues to produce an efficient circulation in these newborn pups. This too is advantageous to the organism: it allows it to "live" at a low circulatory efficiency for long periods of anoxia. In sharp contrast, the adult's circulatory efficiency during an anoxic episode is very efficient during the early phases, but then suddenly collapses at the end. It does not exhibit the long slow tapering-off characteristic of the newborn.

TABLE II.—ATTEMPTED RESUSCITATION OF NEWBORN PUPS

No.	Effect of attempted resuscitation	Start tracheal insufflation at:		
		Time	Minutes after last gasp	Blood pressure
1	Lived	16:53*	3:33	8.1/6.0
2	Lived	17:15	4.01	8.2/7.1
3	Lived	18:22	6:07	7.3/4.1
4	Died	21:50	6:12	5.5/5.0
5	Died	22:00	6:12	5.5/4.7
6	Lived	22:28	6:00	10.7/4.9
7	Lived	22:49	3:31	12.7/11.3
8	Lived	26:20	10:24	5.2/3.7
9	Died	26:58	10:10	7.3/4.8
10	Died	27:58	11:38	2.4/1.8
11	Died	31:40	12:56	6.5/4.0

*To be read: 16 minutes and 53 seconds after start of anoxia, etc.

In the adult, anoxia of moderate grade accelerates respiration but that of high grade for the most part arrests it. In the newborn, the reaction in response to extreme anoxia is one of slow gasping. In the present experiment, with the pups breathing pure nitrogen, only the response to extreme anoxia was observed. The very slow respiratory rate was evidently unable to rid the pup of accumulating carbon dioxide, for its tension rose rapidly and markedly. It is for this reason that the death process resembles closely that of obstructive asphyxia in the adult. It does not resemble acute anoxia or progressive anoxia in which carbon dioxide, because of hyperventilation, is "blown off." The marked accumulation of carbon dioxide in the pups evidently does not stimulate respiration, as it does in the adult, as many have observed.

Circulatory failure in the pups followed respiratory arrest by some 5 to 10 minutes (Table II). Again, this differs considerably from adult behavior, in which circulatory failure usually takes place at about the same time as respiratory arrest. When cerebral failure—that is, an anoxic cerebral insult—takes place with reference to respiratory and circulatory failure was not ascertained in this experiment. In the newborn guinea pig, cerebral insult occurs quite soon after the onset of anoxia, while in the rabbit it is quite late.

This is not an unexpected result, since guinea pigs are born in such a mature state.

The shift in acid base equilibrium is toward a pronounced uncompensated metabolic acidosis. Blood acidities were found to be at *p*H 6.6 approximately—values far lower than found in adults in extreme asphyctic and acidotic states. A hydrogen ion concentration of the order of 6.6 or less makes the computation of carbon dioxide tensions by the conventional methods somewhat unrealistic; nevertheless, they are presented in Table I for what they are worth. Similar changes, except less violent, are well known for asphyxia of the newborn infant. This similarity encourages us to think that study of these reactions in newborn pups may illuminate some of the dark corners in our knowledge of asphyxia neonatorum.

The acidosis is due not only to an uncompensated carbon dioxide excess, this being caused by the low respiratory rate, but also very probably to accumulation of organic acids, particularly lactic and pyruvic. The latter two acids reflect the relative anaerobiosis of the newborn. During the process of anoxic death, these acids pre-empt much of the available alkali reserve, resulting in the demonstrated decreased carbon dioxide content and hypercapnia. Then as the pups advance further along in the process of death, with the continuous production of more carbon dioxide, the carbon dioxide again rises. The total picture represents an animal whose acid-base balance is far less stable than the adult; it is that of an animal which may be pushed into extraordinary extremes of acidosis. We suspect, from the available data on resuscitability that the newborn can recover from these extreme acidoses, but the matter demands more study.

Individual variation in reactions of the pups to anoxia was marked. The same is true for the adult. The situation presents a perennial problem in studying resuscitability, for it means that the length of anoxia, taken alone, does not give an accurate picture of a given pup's condition. The problem was solved for adult dogs by demonstrating that the systolic blood pressure gives an accurate index of the threshold of death. Further study of anoxia in the pups will, it is hoped, reveal a similar sharp objective measurement of this critical physiologic point in the process of death.

SUMMARY

The process of death from anoxia (breathing nitrogen) was studied in newborn pups 3 or 4 days old, simultaneous observations being made of the blood pressure, heart rate, electrocardiogram, breathing, blood gases, and acidity. A pronounced bradycardia and hypotension result, with blood pressures declining to about 23/18 at 10 minutes and 11/8 at 20 minutes. The anoxic pups may readily be resuscitated even though the blood pressure has fallen to 8/6. Breathing slows to about one-tenth the normal rate immediately after the induction of anoxia and then slowly tapers off to cease at about 20 minutes. Circulation stops some 5 or 10 minutes after respiratory arrest. The slow respiratory rate results in the accumulation of much carbon dioxide in the blood, with carbon dioxide tensions finally rising to 100 to 150 millimeters of mercury. The hydrogen ion concentration at death is about 6.6. The type of death is asphyctic, with extreme, uncompensated metabolic acidosis. Great individual variation in reaction occurred. The process of death in the newborn is contrasted with that of the adult, and the adaptive significance of some of the reactions is discussed.

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CARCINOMA OF THE BREAST

A Surgical Follow-Up Study

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TO determine our results in the surgical treatment of carcinoma of the breast and to test the reliability of various criteria of operability and prognosis in this disease, a detailed review has been made of all cases of carcinoma of the breast treated at the Hospital of the University of Pennsylvania during the 20 year period from 1924 through 1943. A minimum of 5 years' follow-up, and in most instances much longer follow-up, has been possible for each of the 1,034 patients treated during this 20 year span. For each patient a master sheet similar to that used by the Presbyterian Hospital group (8, 9) has been completed, and as detailed a follow-up as possible obtained in each case by letters to family physicians, other hospitals and sources of vital statistics, and personal interviews with patients. Some difficulty was encountered in obtaining details of treatment and follow-up data for patients treated more than 20 years ago. The data on the master sheets have been transferred to punch cards for sorting by tabulating machines to facilitate the determination of various correlations.

The material. The 1,034 patients have been grouped into 807 primary and 227 secondary cases depending upon whether previously treated elsewhere for carcinoma of the breast. The 807 primary cases have been further separated by date of admission to this hospital into four 5 year periods: 132 cases for the period from 1924 to 1928, 180 from 1929 to 1933, 200 from 1934 to 1938, 293 from 1939 to 1943; 2 cases were not coded.

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There is apparent a steadily increasing frequency of admissions for this condition as noted in the statistical studies of Shimkin.

Age distribution of patients. In Table I the age distribution of patients with carcinoma of the breast at the time of admission to the Hospital of the University of Pennsylvania is given in 5 year brackets from under 30 to over 75 years of age. Included are the percentage of the whole series represented by each 5 year age bracket, the number of women in the United States according to the 1940 census in the same 5 year bracket, and the case occurrence of carcinoma of the breast per 100,000 female population.

The occurrence of 18 cases in patients under 30 years of age, 1.7 per cent of this series, agrees well with the 2 per cent occurrence given by deCholnoky in his collected series. In our series there is a peak incidence of cases in the 45 to 49 age bracket in accord with other reports. Graphic representation of the case occurrences of carcinoma of the breast per 100,000 women gives a largely unimodal curve with the peak in the 55 to 59 year age bracket. There is a suggestion of bimodality in the slight secondary rise in the 65 to 69 year age bracket which may not be significant. Pack and LeFevre found their case occurrence peak in the 60 to 64 year age bracket. The tapering off of the curve is probably related to the relative infrequency of older patients in a hospital series of breast carcinoma patients compared to the frequency in the general female population.

For the 1,034 patients in this series, marital status, number of pregnancies, and menstrual histories have been recorded insofar as available. The findings are in conformity with the averages for the general population and fail to show any unusual relationships. Figures for

TABLE I.—AGE DISTRIBUTION OF ALL CASES OF CARCINOMA OF THE BREAST IN THIS SERIES

Age bracket, years	No. of cases	Per cent of all cases in series	U. S. female population, 1940 census	Case occurrence of breast cancer per 100,000 U.S. women
Under 30	18	1.7		
30–34 incl.	34	3.3	5,200,000	.65
35–39	89	8.7	4,800,000	1.85
40–44	123	12.0	4,400,000	2.80
45–49	171	16.7	4,000,000	4.28
50–54	153	14.9	3,500,000	4.37
55–59	143	13.9	2,800,000	5.11
60–64	104	10.1	2,300,000	4.52
65–69	90	8.8	1,900,000	4.74
70–74	52	5.0	1,300,000	4.000
Over 75	49	4.8	1,400,000	3.50
Unknown age	8	0.8		

lactation history have been obtained too infrequently to permit any valid conclusions. Where information has been available, 343 women had not reached menopause at the time of admission for breast carcinoma, and 465 had reached menopause.

Symptomatology. Of the 1,034 patients in the series, 975 or 94.3 per cent discovered the breast lesion themselves, 22 lesions were discovered by previous examiners, and 37 lesions were found on admission to the hospital. This finding again emphasizes the fact that most breast cancers are discovered by patients, and not physicians, and that early detection of breast carcinoma still depends principally upon public instruction in periodic self-examination of the breast and in the possible significance of a breast lump. Because of this finding women outpatients at the the Hospital of the University of Pennsylvania are given an instruction sheet outlining the proper method of self-examination of the breast and recommending that this be carried out once every 2 months.

In Table II the presenting symptomatology of the patients in this series is given. Noteworthy is the fact that about half of the patients had no pain whatever and that those who did complain of pain in the breast or axilla considered it mild, transient, or intermittent.

Location of the lesion. Of 807 primary cases of breast carcinoma, the lesion was situated in the right breast in 371, in the left in 423, in both breasts in 10, and not indicated as to laterality in 3. The greater frequency of left-sided lesions is in accord with the reports of others. The quadrant principally occupied by the lesion is indicated in Table III.

The percentages in our series agree generally with those taken from reports in the literature by Ackerman and del Regato and by Geschickter.

Symptom duration before hospital treatment. The studies by 5 year periods of the time interval between the onset of the first symptom of breast carcinoma and the admission of that patient to the hospital for treatment indicate an encouraging but slow improvement. Whereas in the 1924 to 1928 period, only 0.8 per cent of the patients reported in less than 2 weeks from the onset of symptomatology and 5.8 per cent in less than 1 month, in the 1939 to 1943 period these percentages had risen to 12.2 per cent and 23.3 per cent respectively. Conversely, whereas in the 1924 to 1928 period, 22.0 per cent of the patients were admitted with symptoms of over 12 months in duration, this situation obtained in the 1939 to 1943 period in 9.5 per cent.

Analysis of the reasons for this delay shows that negligence on the part of the patient remains apparently the most important cause for delay. The delay by reason of negligence on the part of the patient has shown a steady drop by 5 year periods. Negligence or poor advice by physicians has shown no improvement over this 20 year study though in fairness it must be pointed out that intensive cancer detection and education drives have been stressed increasingly since 1944.

When duration of symptoms is correlated with the age groups of the patients, the only remarkable finding is that a much higher percentage of those who had symptoms of breast carcinoma 2 years or longer were 65 years of age or older. Of the 35 to 39 year group 2.7 per cent had symptoms for 24 to 35 months, 5.3 per cent for 36 months or more; of the 70 to 74 year group 6.8 per cent for 24 to 35 months, 15.8 per cent for 36 months or more; of those over 75 years old 12.2 per cent had symptoms

for 24 to 35 months, 22 per cent for 36 months or more.

The converse is not apparent; the younger age groups did not report for treatment significantly earlier than the older age groups. In all age groups except those over 70 years old, approximately 50 to 55 per cent of patients came to the hospital within 6 months of the onset of symptoms, and this applied to the group 34 years of age and younger.

TREATMENT

Of the primary cases of carcinoma of the breast, 679 were subjected to some form of surgical therapy as indicated in Table IV. One hundred and fourteen were referred to radiation therapy because of refusal to permit surgery, hopeless local advancement of carcinoma, or obvious distant metastatic spread of the disease. As one may note from Table IV, a variety of operative procedures were carried out. Twenty-one patients were subjected to local excision of a varying amount of breast tissue around the primary lesion, but less than the whole breast. One hundred forty-nine patients underwent simple mastectomy, with the rationale that the age of the patient was too advanced, that the condition of the patient was too precarious for radical resection of the breast, that the patient's axilla was free of lymph node metastases which numerous studies have indicated is at best an unreliable guess, or that a less aggressive approach to the problem than our modern standards expect might still suffice. During the latter years of the study, however, simple mastectomy was carried out only when radical mastectomy, the procedure of choice, was impossible or too risky. Basic to the advocacy of radical mastectomy in the treatment of carcinoma of the breast is the concept that the carcinoma is initially localized, and later disseminated by lymphatic and less commonly by vascular channels to other areas. If the lesion is localized to the breast, an adequately performed simple mastectomy should completely remove the disease. The difficulty lies in proving without microscopic examination of all available axillary lymph nodes, that the carcinoma is indeed localized to the breast. Geschickter points out that in breast cancers of only 10 to 15 millimeters in diameter with 3 months average symptomatology, axillary metastases have already occurred in 25 per cent of cases. In the series of Haagensen and Stout

TABLE II.—SYMPTOMATOLOGY OF BREAST CARCINOMA PATIENTS ON HOSPITAL ADMISSION

Symptom	Frequency
Localized tumor	961
No localized tumor noted	40
Enlargement of breast	62
Shrinkage of breast	4
Elevation of breast	1
Lowering of breast	10
Generalized hardness of breast	5
No pain in breast	512
Pain in breast	423
Tenderness on pressure	137
Dimpling of skin	39
History of trauma to breast	91
Ecchymosis of skin to breast	7
Redness of skin of breast	85
Ulceration of skin of breast	62
Massive edema of breast	1
Skin nodules	6
Nipple retraction	68
Bloodless discharge from breast nipple	40
Bloody discharge from nipple	40
Itching or burning of nipple	20
Crusting of nipple	25
Axillary tumor	99
Swelling of arm	20
Pain in axilla or arm	99
Supraclavicular tumor	4
Dyspnea	12
Cough	23
Pain suggestive of bony metastases	30
Abdominal symptoms	4
Neurologic symptoms	9
No symptoms of breast carcinoma noted by patient before examination	47
Details of present illness unknown	16

TABLE III.—SITE OF CARCINOMA IN BREAST IN PRIMARY CASES

Site of tumor in breast	This series		From literature	
	No. of cases	Per cent of total cases	Per cent, Ackerman and del Regato	Per cent, Geschickter
Center	75	12.5	22	22
Upper inner quadrant	100	16.6	14	14.5
Upper outer quadrant	312	51.7	47	44
Lower outer quadrant	72	12.0	7	15.2
Lower inner quadrant	43	7.2	2	3.7
Not coded	205			

TABLE IV.—TYPE OF SURGICAL THERAPY CARRIED OUT IN 689 PRIMARY CASES OF BREAST CARCINOMA

	No. of cases
Partial mastectomy	21
Simple mastectomy	149
Simple mastectomy with axillary dissection	77
Simple mastectomy with removal of pectorals	17
Radical mastectomy	417
Details not recorded	8

(9), axillary metastases were present in 43.8 per cent of patients with primary breast lesions less than 20 millimeters in diameter.

Various compromises with the fundamental belief that radical mastectomy should be performed were achieved by removing the available axillary tissue in conjunction with simple mastectomy (77 patients in this series), leaving the lymphatic vessels and nodes between the pectoral muscles and high in the axilla; and by removing the pectoral muscles without removing the axillary contents (17 patients in this series). Though there has been a tendency to return to simple mastectomy in certain circles, the usual 55 to 63 per cent involvement of the axillary nodes of cases in the average clinic is disregarded, the usual inadequacy of roentgenotherapy in dosage commonly employed to free completely an axilla of cancer cells is overlooked, and the known adequacy of radical surgery to accomplish the same in at least 30 to 40 per cent of involved axillae is traded for an operation of lesser magnitude. These arguments apply with even greater force against local excision of the tumor not followed by prompt more radical surgery.

It should be noted in passing that, as in other teaching institutions with residency programs in surgery, the operative procedures mentioned were carried out by a large number of surgeons of varying experience and aggressiveness.

The relative operability (number of cases operated upon divided by number of primary cases) was 84.1 per cent, the absolute operability (number of cases operated upon divided by total number of cases of breast carcinoma seen) was 65.7 per cent. This percentage will vary considerably among clinics depending upon the degree of advancement of the lesions commonly seen in that clinic and the criteria of operability guiding its surgeons.

TABLE V.—FOLLOW-UP OF 417 PRIMARY BREAST CARCINOMA CASES TREATED BY RADICAL MASTECTOMY

	No. of cases
Patients alive after 5 years	180
Patients lost to follow-up before 5 years	16
Patients died under 5 years	222
Operative death	1
Died, cause unknown	4
Died, intercurrent disease, no evidence of persisting breast carcinoma	12
Died, intercurrent disease, evidence of persisting breast carcinoma	7
Died of breast carcinoma	198

FOLLOW-UP

Of the 807 primary cases of carcinoma of the breast 21 were lost to follow-up before 5 years had passed—a 97.4 per cent follow-up. Of the 417 patients with primary cases on whom radical mastectomy was performed, 16 were lost to follow-up by 5 years—a 96.2 per cent follow-up. Until the organization of the Tumor Clinic in the Hospital of the University of Pennsylvania several years ago, only sporadic attempts were made to follow the surgical patients and most of the lost cases fall into this early period.

Inasmuch as experience had indicated that a number of cases of breast carcinoma treated surgically show metastases or local recurrences after 5 years of clinical freedom from evidence of carcinoma, we have chosen to report our statistics as 5 year survivals with and without evidence of carcinoma, and to avoid the use of the term "five year cure."

TABLE VI.—LOCAL RECURRENCES FOLLOWING RADICAL MASTECTOMY

	No. of cases	Per cent
Radical mastectomy	417	
Local recurrences	133	31.9
Without local recurrences	284	68.1

Time of Appearance of Local Recurrences

Postoperative time period	No. of patients	Cumulative per cent by given time
0–11 months	62	47
12–23 months	28	68
24–35 months	23	85
36–47 months	8	91
48–59 months	3	93.5
5 years or over	9	100

The overall picture of follow-up of the primary cases treated by radical mastectomy is given in Table V.

The loss of 16 patients to follow-up has been mentioned. Only 1 patient died within the arbitrary 30 day postoperative period which we have designated for operative deaths. Death occurred for this individual 12 days after operation from a massive pulmonary embolism before the modern emphasis on early ambulation and prophylaxis of venous thrombosis. Of the patients who died during the 5 year postoperative period, despite efforts to obtain as incontrovertible evidence as possible of the presence or absence of breast carcinoma at the time of death, 4 remain without known cause of death.

Local recurrence. Under local recurrence we have included any case of a reappearance of carcinoma in the operative field. Among the 417 radical mastectomies a disturbingly large number of local recurrences, 133 or 31.9 per cent, were found. In Table VI the times of first appearance of these recurrences are divided into 12 month postoperative periods and the cumulative percentage of recurrences by that given time has been calculated.

As expected, the highest percentage of local recurrences is noted within the first year following operation and a decreasing frequency of recurrence is noted thereafter, although local recurrences amounting to 6.5 per cent of the entire group of local recurrences were noted even after 5 years. Analysis of the operative procedures performed indicates that usually a relatively small amount of skin was removed permitting primary closure of the skin flaps, and that in only 31 cases were split thickness skin grafts applied to the operative area. Possibly a more radical skin removal and more routine use of primary skin grafting would have improved these statistics. The series of Lewis and Rienhoff showing an improvement in salvage rate in those subjected to Thiersch grafting contrasted with those primarily closed, is suggestive support to this change in approach. Despite their use of skin grafting in the vast majority of cases, their overall local recurrence rate was 32.2 per cent.

Among the 417 primary cases treated by radical mastectomy, 252 patients or 60.4 per cent developed metastases within 5 years after operation. One hundred and sixty-five patients or 39.6 per cent were clinically free of metastases at that time.

The time of recognition of metastatic disease is given in Table VII along with the cumulative percentage of patients with metastases by that given period. Here also it is noteworthy that the greatest incidence of metastatic spread was found in the first year after radical mastectomy, and the occurrence of metastases in the succeeding years again

TABLE VII.—METASTASES FOLLOWING RADICAL MASTECTOMY

	No. of cases	Per cent
Radical mastectomy patients...	417	
Metastases.....	252	60.4
Free of metastases (5 years)...	165	39.6

Time of Appearance of Metastases

Postoperative time period	No. of patients	Cumulative per cent by given time
0–11 months.....	86	34
12–23 months.....	54	55
24–35 months.....	43	72
36–47 months.....	22	81
48–59 months.....	9	85
5 years or over.....	38	100

TABLE VIII.—FOLLOW-UP OF RADICAL MASTECTOMY CASES BY 5 YEAR PERIODS

	1924–1928		1929–1933		1934–1938		1939–1943		Overall	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Patients with radical mastectomy	66		97		70		183		416	
Local recurrence	28	42	34	35	19	27	59	32	140	33.7
Five year survival	18	27	35	36	36	51	89	49	178	42.8
Five years or longer clinical freedom from carcinoma	16	24	27	28	33	47	71	39	147	35.3

TABLE IX.—RESULTS OF RADICAL MASTECTOMY ACCORDING TO AGE OF PATIENTS

Age group	Under 34		35–39		40–49		50–59		Over 60	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Total cases	25		51		147		120		73	
Local recurrences	9	36	18	35	50	34	38	32	17	23
Metastases	14	56	31	61	94	64	68	56	44	60
Five year survival	8	32	26	51	63	43	49	41	32	44
Five years or more free of carcinoma	8	32	20	39	52	35	41	34	26	35

TABLE X.—TEN MOST COMMON LOCATIONS OF BREAST CARCINOMA METASTASES IN 417 RADICAL MASTECTOMY PATIENTS

Location	No. of cases	Per cent of total
Homolateral axilla	235	56.4
Lungs and pleurae	130	31.2
Bones	99	23.7
Spine	65	
Pelvis	55	
Femur	42	
Ribs	33	
Skull	22	
Homolateral supraclavicular nodes	85	20.4
Liver	75	18.0
Skin	37	8.9
Contralateral axilla	30	7.2
Mediastinal nodes	23	5.5
Upper cervical nodes	17	4.1
Brain	17	4.1

TABLE XI.—OPERABILITY OF PRIMARY CASES ACCORDING TO HAAGENSEN'S CRITERIA

	No. of cases
Operable by Haagensen's criteria	581
Not coded because of inadequate data	13
Inflammatory carcinoma	17
Extensive (more than ⅓) skin edema of breast	49
Satellite skin nodules	43
Preoperative edema of arm	18
Intercostal or parasternal nodules	2
Proved or clinically certain supraclavicular metastases	61
Distant metastases	69
Development of cancer during pregnancy or lactation	7
Presence of two or more of the following: Ulceration of skin, limited edema of skin, fixation of breast to chest wall, axillary nodes over 2.5 cm. in diameter, fixation of axillary nodes to chest wall	108

paralleled the appearance of local recurrences but with a somewhat higher proportion of metastases appearing after 5 years.

When 416 patients on whom radical mastectomy was performed are divided into 5 year periods from 1924 through 1943, a decrease in the incidence of local recurrences and increase in 5 year survivals and 5 year arrests are observed. These figures are shown in Table VIII. The best statistics are found in the 1934 to 1938 period, and probably depend upon its relative smallness. How much increasing selection of cases for radical mastectomy and earlier submission of patients to operation play in the improvement in these statistics has not been determined.

When the results of therapy are studied in the various age groups, no significant variations are noted either in the young or the old (Table IX). This observation is in accordance with the findings of Haagensen and Stout (9). Of particular interest are the results in the group under the age of 34, considering the opinion which continues widespread that the prognosis is unfavorable in the young. The 5 year survival rate and 5 year or longer freedom from clinical evidence of carcinoma are an identical 32 per cent. This finding supports those of deCholnoky who could find no worse a prognosis in patients under 30. His collected percentage of 40.8 five year arrests is better than that in our series. Richards reported a 55 per cent 5 year survival and 36 per cent 10 year survival for treated patients in the 21 to 30 year age group, as against the respective figures of 43 and 26 per cent for his whole series regardless of age. Shimkin and associates find the same percentage 5 year survival for patients under as against those over 50 years of age in Portmann stage I (carcinoma localized to breast), and no significant difference in 5 year survival of patients in stage II (carcinoma involving some axillary nodes).

Location of metastases. When it was possible to determine the location of metastases, these were recorded and the 10 most common locations listed in Table X.

CRITERIA OF OPERABILITY

The diagnostic characteristics of breast carcinoma, as ascertained by physical examination, were recorded for each patient for whom data were available. The physical findings in our series have been considered in retrospect and with the advantage of knowledge of the outcome of the case, in the light of the criteria of operability proposed by Haagensen and Stout (9). The criteria of operability used in this series were not strictly drawn, and cases were accepted for operation on the basis that operation offered a reasonable chance of cure or comfortable palliation. A number of cases considered too advanced for operation by the criteria of Haagensen and Stout were subjected to radical mastectomy, so that the patient might not be denied her slim chance for cure. Of 807 primary cases to

which the criteria of operability of Haagensen and Stout have been applied, the findings suggesting inoperability and their frequency of occurrence are listed in Table XI.

The follow-up of those cases considered inoperable by these criteria is of interest. Of 90 patients falling into one or more of these inoperable groups, and subjected to x-ray therapy or left untreated, only 1 survived just beyond the 5 year mark to die of her carcinoma. Sixty-seven cases subjected to radical mastectomy, 47 subjected to simple mastectomy, and 23 subjected to modified simple mastectomy (simple mastectomy plus partial axillary dissection or simple mastectomy with removal of pectoral muscles without axillary dissection) fell into the categorically inoperable group. Of all these, 16 patients survived 5 years or longer, and 8 were apparently free of breast carcinoma. The preoperative findings suggesting inoperability, the procedure carried out, and the survival period and status of the patients who survived at least 5 years are given in Table XII.

These cases do not vitiate the criteria of operability suggested by Haagensen and Stout; in fact, they tend to confirm them remarkably well in many respects. The cases do, however, show that too rigid an adherence to these criteria, which were in some instances established on rather small subgroups, will result in a denial of a radical procedure to a patient who might otherwise be "cured." Certainly one cannot justifiably criticize the surgeon who has performed a radical mastectomy simply because he has not strictly adhered to their criteria.

Stage classification of carcinoma of the breast. Richard's stage classification of breast carcinoma has been reproduced in Table XIII. This classification presents the advantages of separation of cases with axillary metastases into several groups in which there is demonstrable difference in prognosis and in which a more detailed separation is made of local lesions on the basis of size and skin changes. It has been possible to apply this classification to 413 of the patients with primary breast carcinoma on whom radical mastectomy was performed, and the results are indicated in Table XIV with the follow-up in each group as regards survival and freedom from clinical evidence of carcinoma.

TABLE XII.—ANALYSIS OF SURVIVALS OF CATEGORICALLY INOPERABLE CASES, ACCORDING TO CRITERIA OF OPERABILITY OF HAAGENSEN AND STOUT

Radical Mastectomy	
No. of cases	67
No. of 5 year survivals	7
1. Satellite skin nodules	Died at 5 yr. of intercurrent disease
2. Satellite skin nodules	Died at 9 yr. of breast carcinoma
3. Distant metastases	Died at 9 yr. of breast carcinoma
4. Skin ulceration and limited edema of skin	Died at 6 yr. of breast carcinoma
5. Limited skin edema and axillary nodes over 2.5 cm. diameter	Died at 10 yr. of breast carcinoma
6. Fixation of axillary nodes to chest wall and nodes over 2.5 cm. diameter	Died at 15 yr. of mesenteric thrombosis, no evidence of carcinoma at autopsy
7. Skin ulceration and limited edema of skin	Died at 7 yr. of breast carcinoma
Total No. free of original carcinoma	2
Simple Mastectomy	
No. of cases	47
No. of 5 year survivals	8
1. Skin ulceration and limited edema of skin	Died at 7 yr. of breast carcinoma
2. Skin ulceration and limited edema of skin	Died at 8 yr. of carcinoma of the sigmoid
3. Skin ulceration and limited edema of skin	Alive at 12 yr.
4. Skin ulceration and limited edema of skin	Died at 12 yr. of apoplexy
5. Skin ulceration and limted edema of skin	Died at 16 yr. of sarcoma of uterus
6. Skin ulceration and limited edema of skin	Alive at 5 yr.
7. Fixation of axillary nodes to chest wall and nodes over 2.5 cm. diameter	Died at 5 yr. of breast carcinoma
8. Occurrence during lactation	Alive at 12 yr.
Total No. free of original carcinoma	6
Modified Simple Mastectomy	
No. of cases	23
No. of 5 year survivals	1
	Died at 7 yr. of intercurrent disease without evidence of carcinoma

A discouragingly large number of cases, as has been evident in previous tables, fell into the advanced stages of the disease by this classification. It is also obvious that the survival rates in the various stages fell far short of those quoted by Richards, all of whose patients had postoperative radiotherapy. Probably the chief value of this classification lies in its permitting the surgeon to appraise some-

TABLE XIII.—RICHARDS' STAGE CLASSIFICATION OF BREAST CARCINOMA

Stage		Per cent survival from Richards' series	
		5 Year	10 Year
Stage I	Skin—not involved Tumor—localized in breast, movable, 1–3 cm. in diameter Metastases—none in axillary nodes or elsewhere	81	59
Stage II	Skin—not involved Tumor—localized in breast, movable, 3–6 cm. in diameter Metastases—few axillary nodes involved, no other metastases	54	28
Stage III	Skin—attached, dimpled, but not obviously invaded; nipple retraction Tumor—localized in breast, more than 6 cm. in diameter, attached to fascia, but not fixed to chest wall Metastases—few axillary nodes may be present or axillary nodes may not be involved	38	21
Stage IV	Skin—edematous or brawny induration or peau d'orange, or ulceration or local skin nodules or evidences of acute inflammation Tumor—diffuse infiltration or rigid fixation to chest wall or edema of breast Metastases—many axillary nodes may be involved or fixed, no clinical or roentgenologic evidence of distant metastases	16	8
Stage V	Skin—as in any other group or stage or with secondary nodules beyond periphery of breast Tumor—as in any other stage or group Metastases—extensive axillary node involvement or supraclavicular node involvement or clinical or roentgenologic evidence of distant metastases	3	0
	Overall picture	43	26

TABLE XIV.—RESULTS OF TREATMENT OF PRIMARY CASES WITH RADICAL MASTECTOMY CLASSIFIED ACCORDING TO RICHARDS' STAGE CLASSIFICATION

	Stage I		Stage II		Stage III		Stage IV		Stage V	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Total cases	56		86		154		101		16	
Survival less than 1 year	26	46	50	58	101	66	82	81	13	81
1–4 years	4	7	5	6	13	9	8	8	1	6
5 years or more	26	46	31	36	40	26	11	11	2	13
Freedom from evidence of carcinoma less than 1 year	32	57	58	68	119	73	88	87	16	100
1–4 years	0	0	4	5	3	2	1	1	0	0
5 years or more	24	43	24	28	32	21	12	12	0	0

what more precisely, with a breast lesion of given characteristics, the odds of that patient's surviving 5 years and remaining free of carcinoma at that time. It also affords a more rigid classification of breast carcinoma for comparison of results in various series.

Richards has also proposed a clinical index of malignancy modified from the original index proposed by Lee and Stubenbord. This index is given in Table XV with weighting factors, gradation factors, and the formula for calculation. To date this clinical index of malignancy has not been used as a guide, but, in retrospect application, our therapy in certain cases would likely have been changed had it been applied.

Richards' clinical index of malignancy has been calculated for each patient in the radical mastectomy group, and in Table XVI the breakdown according to this yardstick is given for our series.

Again this permits the surgeon to formulate a statistical prognosis of his patient's chances of 5 year survival a little more accurately than merely on the basis of the statistics associated with a single factor—the presence or absence of axillary lymph node metastases. When these statistics are compared with the curve of life expectancy in untreated cases of carcinoma of the breast the results in cases with a clinical index of malignancy above 40 would suggest that the treatment has not prolonged life significantly, and suggest that radical mastectomy has little to offer patients in this group in terms of longevity over intensive radiotherapy.

When the age of the patient with breast carcinoma is correlated with the index of malignancy for that patient's lesion, as in Table XVII, there appears a suggestion that the younger age groups tend to have tumors with a lower index of malignancy.

There is also the possible explanation that many of these younger women with increasing cancer prevention propaganda might have consulted their physicians initially earlier than the older women in whom a fear of hospitalization and greater indifference to cancer pre-

TABLE XV.—RICHARDS' CLINICAL INDEX OF MALIGNANCY

	Weighting factor	Gradation factor
Lactation	L-1	Absent—0 Present—9
Age of patient	A-2	Prior to menopause—1 4 years or more after menopause —2 Concurrent with or up to 4 years after menopause—4
Site of lesion	S-3	Outer quadrant without nodes—½ Inner qudrant without nodes—2 Outer quadrant with nodes —3 Inner quadrant with nodes —5
Rate of growth	R-4	Slow—1 Moderate—2 Fast—3 Inflammatory—4
Stage or extent	E-5	Stage I —1 Stage II —2 Stage III—3 Stage IV —4 Stage V —5

Clinical index of malignancy (CIM) = 1L+2A+3S+4R+5E.

vention drives resulted in their later diagnosis. At least there is no significant trend suggesting that lesions in the young are more malignant.

Simple mastectomy. With regard to the results of treatment of breast carcinoma by simple mastectomy, 148 primary cases (1 lost to follow-up) were followed 5 years at which time 60 patients or 40 per cent were still surviving. In the group of 74 patients (3 lost to follow-up) subjected to simple mastectomy with partial axillary dissection, 33 or 43 per cent were alive at the end of 5 years. These seemingly good results for simple mastectomy with and without partial axillary dissection appear, however, to be based on somewhat different material than that subjected to radical mastectomy. Of the patients subjected to simple mastectomy 67 per cent had lesions clinically confined to the breast (Portmann stage I), whereas of those subjected to radical mastectomy, 50 per cent had lesions clinically confined to the breast. This observation appears to be a reasonable indication of some case selection favoring the less advanced cases for simple mastectomy. When the 5 year survival of patients with radical mastectomy for Portmann stage I lesions is compared to the 5 year survival of patients with simple mastectomy for similarly localized lesions, the percentages are 59.0 per cent and 51.5 per cent respectively.

TABLE XVI.—RESULTS OF TREATMENT OF PRIMARY CASES WITH RADICAL MASTECTOMY CLASSIFIED ACCORDING TO RICHARDS' CLINICAL INDEX OF MALIGNANCY

Richards' clinical index of malignancy	No. of cases	Survival 5 years or more		Freedom from clinical carcinoma 5 years or more	
		No.	Per cent	No.	Per cent
10–29	123	85	69.1	73	59.3
30–39	150	64	42.6	53	35.3
Over 40	135	25	18.6	19	14.1

TABLE XVII.—CORRELATION OF RICHARDS' INDEX OF MALIGNANCY WITH AGE OF PATIENT

Age of patient, years	Index 10–29 Per cent	Index over 40 Per cent
Under 30	44.5	22.7
30–34	50.0	21.4
35–39	48.0	12.0
40–44	37.4	35.6
45–49	33.4	26.2
50–54	16.2	42.6
55–59	19.6	45.2
60–64	27.9	39.2
65–69	8.0	48.0
Over 70	44.5	33.3

PATHOLOGY

In the study of this series of patients, the slides of tissue removed at operation were reviewed, and the pathologic features of each case itemized on master sheets to permit, insofar as possible, further correlations with survival rates.

Muscle and fascial involvement. When the survival of patients who presented evidence of direct invasion of the pectoral fascia or muscle by the tumor were studied, none of the 17 in this group survived more than 1 year after operation. Although this is a very small group, the fact that all succumbed so soon after radical mastectomy still suggests that invasion of pectoral fascia or muscle lends an exceedingly poor prognosis.

Skin involvement. On microscopic examination of breast carcinoma, the lesions of 69 patients presented evidence of involvement of the skin. Of these, 38 or 57 per cent were

TABLE XVIII.—CORRELATION OF CERTAIN PATHOLOGIC FINDINGS WITH SURVIVAL AND FREEDOM FROM CLINICAL EVIDENCE OF BREAST CARCINOMA IN RADICAL MASTECTOMY PATIENTS

Pathologic findings	No. of cases	5 year survival		5 year clinical freedom from carcinoma	
		No.	Per cent	No.	Per cent
Tumor involvement of pectoral muscle or fascia	17	0		0	
Tumor involvement of skin	69	38	57	28	41
Diffuse involvement of breast by tumor	6	0			0
Multiple discrete carcinomas of breast	7	2	29		0

alive at the end of 5 years after radical mastectomy and 28 or 41 per cent were free of clinical evidences of carcinoma. Apparently the presence of microscopic skin involvement does not substantially affect the prognosis.

Multiplicity of tumors. Seven primary cases presented multiple discrete carcinomas of the breast. Two patients survived radical mastectomy 5 years, 1 dying before 6 and the other before 7 years of persistent carcinoma. Since all patients died of breast carcinoma, despite the smallness of the group, it seems likely that multiplicity of primary tumors lends a poor prognosis. Six patients presented diffuse involvement of the breast and none survived 5 years. The conclusion is similar.

Size of tumor. When the gross pathologic measurement of the greatest diameter of the tumor was made and these findings were correlated with 5 year survival and freedom from clinical evidence of carcinoma, the results are shown in Table XIX. Lesions under 20 millimeters in greatest diameter permitted an 84 per cent 5 year survival and 74 per cent freedom from clinical evidence of carcinoma at 5 years. At the other extreme, lesions over 90 millimeters in greatest diameter permitted only 1 survival beyond 5 years after operation without evidence of persisting breast carcinoma. The former figures undoubtedly represent the earlier lesions and again evince the value of early diagnosis and thorough treatment.

TABLE XIX.—CORRELATION OF SIZE OF BREAST TUMOR IN PRIMARY CASES WITH RADICAL MASTECTOMY WITH FIVE YEAR SURVIVAL AND 5 YEAR CLINICAL FREEDOM FROM CARCINOMA

Size of tumor, mm.	No. of cases	5 years or more survival		5 years or more freedom from evidence of carcinoma	
		No.	Per cent	No.	Per cent
Under 20	38	32	84	28	74
20–49	235	101	43	79	33
50–89	76	22	29	18	24
Over 90	7	1	14	1	14

An attempt was made to classify the breast carcinomas into histologic types as indicated in Table XX. No attempt was made to differentiate between scirrhous and medullary forms inasmuch as many tumors show areas of both types depending upon the fibrous tissue density and hyalinization of the mammary tissue being invaded by the tumor.

Most of the carcinoma cells showed no special characteristics enabling the pathologist (H.T.E.) to separate such a tumor from the general run of breast carcinomas. No significant difference in duration of symptomatology with one or another histologic type was found in the correlations run. When, however, correlations were made between histologic type and 5 year survival, the survival of the colloid and strictly intraductal types is found to be roughly twice, and that of the papillary type roughly one and a half times that of the remaining types of breast carcinoma. The correlations were approximately the same whether simple or radical mastectomy had been performed on the breast in the intraductal and colloid types, and as expected, somewhat poorer survivals were recorded in simple than in radical mastectomy patients in the other major histologic types. Colloid carcinoma occurs in from 1.66 per cent to about 5.8 per cent of cases. Warren reports that in his experience large and bulky mucinous carcinomas of the breast with ulceration of the skin may be entirely free of axillary metastases and amenable to surgical removal. Haagensen finds a similarly favorable prognosis for mucinous degeneration of breast carcinoma. Ges-

chickter points out that gelatinous and comedocarcinomas usually grow slowly and metastasize late. Haagensen reports a similar benignancy of papillary adenocarcinoma which he ascribes not to the fact that the bulk of the tumor is intracystic, but to the fact that it shows minimal anaplasia. Again for the comedo (strictly intraductal) type, though he found no significantly different prognosis from the run of breast carcinomas, the individual patients dying before 5 years lived twice as long as similar patients with other types of breast carcinoma. The findings of no significantly different prognosis for very large and very small cell carcinomas agrees with the careful studies of Greenough, and differs from the favorable impression of the small cell type Haagensen has expressed. The relative benignancy of the mucinous types of carcinoma of the breast is also discussed by Simpson.

Axillary metastases. Unfortunately in many instances the axillary tissues were unavailable for pathologic examination, but where present, as indicated in Table XXII, of 235 radical mastectomy patients with involved axillary nodes, 73 patients or 31.1 per cent survived 5 years and 53 or 22.5 per cent were free of clinical evidence of carcinoma 5 years or more. Of 145 radical mastectomy patients in whom no axillary metastases were demonstrated, 109 or 75.2 per cent survived 5 years and 88 or 60.6 per cent were without clinical evidence of carcinoma 5 years or more after mastectomy. These figures represent the cumulative results of the entire 20 years of surgical treatment of breast carcinoma, and the overall average is consistent with the more recent salvage rates from leading clinics around the country. Corresponding Mayo Clinic figures for 5 year survival, reported by Harrington recently are as follows: among 4,331 radical mastectomy patients with axillary metastases at operation, 1,406 or 32.5 per cent survived 5 years; among 2,994 radical mastectomy patients without axillary metastases at operation, 2,344 or 78.3 per cent survived 5 years. Hospital of the University of California statistics reported by Shimkin and associates show that of 246 radical mastectomy patients without axillary metastases, 158 or 75.2 per cent were surviving at 5 years; and of 375 patients with axillary metastases (Portmann stages II, III, and IV) subjected to radical mastectomy, 122 or 32.5 per cent survived 5 years. Memorial Hospital statistics given by Adair show that from 1920 through 1936, in primary operable cases of breast carcinoma subjected to radical mastectomy, 305 of 424 patients, or 71.9 per cent, without axillary metastases survived 5 years; 228 of 588 patients, or 38.8 per cent, with axillary metastases survived 5 years. It is to be noted that 87.4 per cent of the Memorial Hospital group with axillary metastases received irradiation in addition to radical surgery. In comparison with these statistics, those in our series are neither better nor worse by a sufficient margin to be statistically significant.

TABLE XX.—HISTOLOGIC TYPES OF BREAST CARCINOMA IN PRIMARY CASES

	No. of cases
Pathologic sections not available	172
No special histologic type	423
Papillary	23
Intraductal (without invasion of surrounding breast)	26
Pagetoid	7
Large cell	114
Small cell	33
Clear cell	5
Spindle cell	5
Squamous cell	15
Colloid	27
Other types	12

Tumor in the axillary fat. When 196 patients with axillary metastases but no tumor in the axillary fat were compared prognosti-

TABLE XXI.—CORRELATION OF HISTOLOGIC TYPES OF BREAST CARCINOMA WITH SURVIVAL AND FREEDOM FROM CLINICAL EVIDENCE OF CARCINOMA IN PRIMARY CASES WITH RADICAL MASTECTOMY

Histologic type	Survival 5 years or more		Freedom from clinical evidence of carcinoma 5 years or more	
	No.	Per cent	No.	Per cent
No special type	109	42.5	88	34.2
Large cell	31	38.7	27	33.8
Small cell	6	38.0	5	31.0
Intraductal	11	73.4	10	66.4
Colloid	12	75.0	10	62.5
Papillary	13	54.2		

TABLE XXII.—CORRELATION OF PRESENCE OR ABSENCE OF AXILLARY METASTASES WITH SURVIVAL AND FREEDOM FROM CLINICAL EVIDENCE OF CARCINOMA FOR 5 YEARS IN PRIMARY CASES TREATED BY RADICAL MASTECTOMY

5 year survival:
With axillary metastases, 73—31.1 per cent of 235 cases
Without axillary metastases demonstrated, 109—75.2 per cent of 145 cases

5 year or more clinical freedom from breast carcinoma:
With axillary metastases, 53—22.5 per cent of 235 cases
Without axillary metastases demonstrated, 88—60.6 per cent of 145 cases

cally with 78 cases showing axillary metastases with tumor invading the axillary fat, the 5 year survival rates for both groups were an identical 29 per cent. Apparently invasion of axillary fat beyond the capsule of a lymph node has no significant effect on 5 year survival.

Lymph and blood vessel invasion. In the microscopic examination of slides of each breast tumor, search was made for evidences of lymph vessel invasion in the breast by the carcinoma. Where such was evident, 5 year survival was 30.4 per cent and freedom from clinical evidence of carcinoma for 5 years or more 21.2 per cent. Where no such invasion was seen, the respective percentages were 53.3 and 43.7 per cent. Probably if additional sections would have been available for more thorough examination, some of those considered free of evidences of lymphatic invasion would be found harboring tumor in lymphatic vessels. Search was simultaneously made for tumor invading blood vessels, and, as might be expected, where found this proved to be prognostically bad. Three of 17 cases survived 5 years and only 1 of these was free of clinical evidences of carcinoma. Delbet reported 26 such cases all dead within 4 years of operation. Of course this type of metastatic spread remains unsolved by any approach to carcinoma of the breast.

Nerve sheath involvement. Of 9 patients in whom nerve sheath involvement was demonstrated microscopically, 2 survived 5 years but only 1 patient was free of clinical evidence of breast carcinoma. These are too few cases to be significant, and this is likely a late manifestation of breast carcinoma.

Degree of differentiation. An attempt was made on microscopic examination to judge the degree of differentiation of the breast carcinoma, in a manner akin to other estimations of degree of malignancy, on the bases of degree of simulation of normal breast histology by the carcinoma particularly in adenomatous arrangement of tumor cells, of the degree of variation in size and shape and hyperchromatism of the nuclei, and of the number of mitotic figures per high power field. As many sections as were available have been examined to determine the fundamental and predominant characteristics of the tumor. Only 3 classes have been used—well, moderately well, and poorly differentiated—and into these the radical mastectomy specimens have been placed. As expected, patients with well differentiated lesions, which are usually slow-growing and slow to metastasize, showed 80 per cent 5 year or longer survival after radical mastectomy and 83 per cent after simple mastectomy. With poorly differentiated lesions the respective percentages fell to 28.2 per cent and 26 per cent. Greenough divided his series similarly into three groups on the basis of differentiation and showed similar results.

TABLE XXIII.—CORRELATION OF DEGREE OF DIFFERENTIATION OF BREAST CARCINOMA WITH 5 YEAR SURVIVAL OF PRIMARY CASES TREATED BY SIMPLE AND RADICAL MASTECTOMY

Differentiation	Radical mastectomy cases Per cent	Simple mastectomy cases Per cent
Well differentiated	80.0	83
Moderately well differentiated	50.9	54
Poorly differentiated	28.2	26

SUMMARY

The results in 807 primary cases of carcinoma of the breast, with particular emphasis on the analysis of the results in those treated by radical mastectomy, have been presented.

In general, it may be concluded that the criteria of operability set forth by Haagensen and Stout are fairly well but not absolutely supported in their retrospect application to this series of cases. Some instances of salvage in the combined presence of skin ulceration

and limited edema of the skin make one regard this as a somewhat less dire prognostic finding. The liberal rather than strict application of their criteria will result in the salvage of an occasional additional breast carcinoma patient and, in the authors' opinion, is worth while.

Classification of the breast carcinomas by Richards' stage classification and by his clinical index of malignancy enables one to predict with greater accuracy than by the choice of any single pathologic feature the odds of a patient's surviving 5 years and of then being free of evidences of breast carcinoma.

Pathologically, evidence is again presented that papillary, strictly intraductal, and colloid carcinomas have a much better prognosis than the general run of breast carcinomas. Poor prognoses are associated with diffuse involvement of the breast, multiple carcinomas of the breast, involvement of the pectoral fascia and muscle, and blood vessel invasion. Microscopic involvement of the skin and invasion of the axillary fat from involved lymph nodes seem not to affect prognosis. Several forms of indirect evidence that carcinoma in the young affords no worse a prognosis than in any other age group, are presented.

The results of simple mastectomy, even though applied to a series of cases with less far advanced disease than those to whom radical mastectomy was applied, have failed to prove as beneficial as the results of radical mastectomy. Radical mastectomy is deemed unquestionably the best treatment for operable carcinoma of the breast and cannot, with 1 operative mortality in 417 radical mastectomies, be considered other than a relatively safe treatment.

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THE CONTROL OF TROMEXAN THERAPY

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THE value of anticoagulants in the prophylactic and active treatment of thromboembolic conditions has been well established. The hazards of such therapy under a well controlled routine, including proper laboratory facilities, are minimal, and the reduction in mortality and morbidity as result of thromboembolic complications in both medical and surgical conditions has been noteworthy. Until recently, dicumarol was the only prothrombin depressing drug available, and because of the many reported cases of serious bleeding following its use, not a few of them fatal, many clinicians have been wary of it. The slow induction period and slower recovery period made an overdose of the drug dangerous and in some instances difficult to counteract. In recent years tromexan (ethyl biscoumacetate) has been favorably reported upon and, particularly because of its short recovery period, from the point of view of the bleeding danger, has been considered a better drug than dicumarol.

Inasmuch as a number of investigators have reported rather extensively on the use of both dicumarol and tromexan with few or no cases of serious bleeding in the case of either drug, it would appear that the control may be the most important factor in the use of any accepted anticoagulant and would account for the variation in the many reports up to the present time. However, since, for the most part, the same methods have been used for the control of tromexan therapy as for that of dicumarol, certain advantages of tromexan would seem to be inherent in the drug. It is the purpose of this paper to report experience with tromexan in 135 patients and to emphasize certain apparent points of importance in the administration of the drug.

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METHODS

One stage and two stage prothrombin determinations were run in parallel. The one stage test was carried out on whole plasma after the technique of Quick and associates with the exception that soluplastin was used as thromboplastin in place of acetone-dried rabbit brain. The material was tested each day for potency and a time of 11 seconds (±0.2) recorded before it was used. The saline-dilution control curve was run each week on normal plasma. The different lots of soluplastin are surprisingly uniform in activity and their curves vary no more than those made with acetone-dried rabbit brain. Duplicate readings were made on each blood sample and were required to check within 0.2 second. The two stage test was the original method of Warner, Brinkhous, and Smith, as modified by Ware and Seegers.

In addition to these tests, a number of bloods were examined for Ac-globulin and antithrombin activity the results of which will be the subject of a separate report.

MODE OF ADMINISTRATION

Single doses. In order to determine the effects of a single dose of tromexan from the points of view of speed and degree of induction and recovery 12 patients were given such doses, varying from 1,200 to 2,400 milligrams. The tromexan was given about 8:00 o'clock in the evening and blood samples drawn for prothrombin determinations the following morning around 9:00. Samples were again taken around 1:00 and 6:00 p.m. of that day and again around 8:00 a.m. the following day. Subsequent determinations were made daily or on alternate days for in some instances as long as 14 days.

MAINTENANCE THERAPY

One hundred and sixteen patients with various types of intravascular clotting were placed on continuous tromexan therapy. In-

cluded in the group were patients with thrombophlebitis, pulmonary embolism, peripheral arterial embolism, coronary thrombosis, central retinal vein thrombosis, and the postphlebitic syndrome. Included in the count of 116 are 3 patients in whom the drug was used prophylactically. In some instances heparin was used in the early part of the induction period before the tromexan had reduced the prothrombin to the therapeutic level. The heparin was given intravenously at intervals of 4 hours, and blood samples for prothrombin determinations were drawn at least 6 hours after the last dose of heparin. This is essential to the accuracy of the tests for tromexan effect. The periods of therapy varied from 4 days to 1 year, 6 months, and 20 days, the average being 61 days. Twenty-four patients received the drug for longer than 3 months, 4 longer than 6 months, and 4 patients were treated for more than a year. After an initial prothrombin level had been obtained, tromexan was administered by mouth the usual initial dose being 1,800 milligrams. In most instances, this was given about 5:00 p.m. and a blood sample for prothrombin determination was drawn the following morning between 8:00 and 10:00. On the second day, 1,200 milligrams of tromexan were given in the late afternoon or early evening, and blood for prothrombin determination drawn the following morning. From this point, the determinations were made as indicated by the subsequent prothrombin levels. In most instances, tests were made daily for the first week of therapy. In cases of prolonged therapy, the frequency of determinations was reduced to twice a week, then once a week, and finally biweekly tests were made. For reasons of safety the interval was never purposely extended to beyond 2 weeks. In most instances, a single daily dose of tromexan was given. In some patients, however, it was necessary to use divided doses (i.e., morning and evening) in order to stabilize the prothrombin level within the therapeutic bracket.

A two stage level of between 10 and 30 per cent was considered desirable. As noted in previous reports (4, 5, 6), the one stage test, except in the induction period, is usually higher than the two stage test, and the prothrombin as measured by the two stage test has been the figure dictating the dose of tromexan. When the prothrombin dropped to below 10 per cent as measured by the two stage method, the dosage of tromexan was reduced. Usually the level of the one stage in such instances was above 10 per cent, indicating that factors other than prothrombin were compensating for the lower level of that factor and thus acting as a safeguard against bleeding. When the prothrombin, according to both tests, was below 10 per cent, tromexan was stopped until one or both tests showed the prothrombin to be above 10 per cent. As will be pointed out later, the success of tromexan therapy depends on regular daily dosage, and the omission of the drug on one day may result in the rise of the prothrombin to a level considerably above the therapeutic bracket and a danger of recurring thromboembolism.

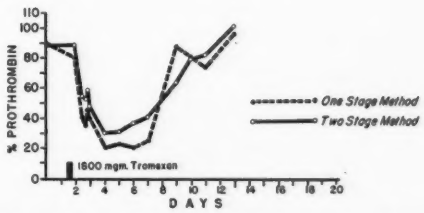

Fig. 1. This chart represents the changes in the prothrombin levels of a patient as measured by the one stage and two stage methods after the administration of a single dose of 1,800 milligrams of tromexan. A therapeutic level was reached 60 hours after the drug was given and the prothrombin had returned to normal 9 days later. The induction period is, as a rule, shorter than this when a second dose is given 24 hours following the original one. Likewise, the recovery period is shorter for most patients on maintenance therapy. The above pattern is reasonably representative of the response to single doses of 1,500 milligrams or more. In this instance with the exception of the ninth day the 2 prothrombin methods follow each other closely.

Seven patients suffering from conditions other than thromboembolism were placed on dipaxin (an indandione prothrombin depressant), tromexan, and dicumarol in succession and in that order, and maintenance therapy established in each case. Sufficient time was allowed between the withdrawal of one drug and the administration of the next to permit the prothrombin to return to pretherapy levels. This method provided for the com-

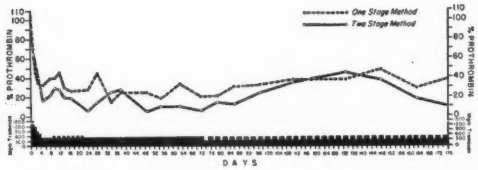

Fig. 2.

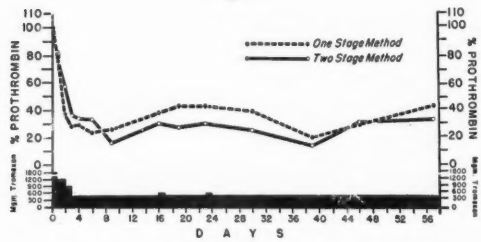

Fig. 3.

Figs. 2 and 3. The above figures represent the courses of patients on maintenance therapy. They show a prompt response to the drug, an early therapeutic control, and reasonably uniform prothrombin levels over a period of weeks. It is important that the drug be continued when the prothrombin has reached therapeutic levels. In these patients the one and two stage methods correspond reasonably well. In the early days the one stage usually shows a more rapid drop and then returns to a somewhat higher level than the two stage. Because it leaves uncontrolled a number of factors which may compensate for a low prothrombin it is an important measure of safety when the two stage shows a level below 10 per cent.

parison of the three drugs, particularly from the point of view of the induction periods in the same patients.

RESULTS

Single doses. Of the 12 patients receiving a single dose of tromexan, the original prothrombin level varied from 88 to 113 per cent, the average being 100. Three were given 1,200 milligrams each. The lowest prothrombin level reached in any of these was 53 per cent (original 113) and was recorded 60 hours after the drug was given. In the 2 other patients the level dropped from 109 and 113 to 76 and 78 per cent respectively at 15 and 23 hours after the ingestion of the tromexan. Three patients were given 1,500 milligrams each, and their prothrombin levels were reduced from 101, 96, and 96 to 53, 41, and 46 per cent 26 hours later. In the latter case it dropped to 43 per cent at the end of the next 24 hours. Two patients taking 1,800 milligrams showed drops of from 95 and 88 per cent to 43 and 31 per cent at 12 and 61 hours respectively. Two patients receiving 2,100 milligrams each had respective prothrombin drops of from 97 and 100 per cent to 32 and 59 per cent at 10 and 7 hours. Two patients receiving 2,400 milligrams each had prothrombin falls of from 97 and 100 per cent to 33 and 31 per cent at 12 and 37 hours respectively. The level of the first patient, 4 days after the tromexan was given, was still 33 per cent. The other was followed for 10 days and the prothrombin had returned to only 52 per cent at that time.

Patients receiving single doses of 1,200 milligrams or less for the most part returned to near normal levels after 3 to 4 days. Those who were given 1,500 milligrams or more required from 3 to 8 days to return to normal after the nadir, and, as noted before, 1 patient who received 2,400 milligrams still had a level of 52 per cent at 10 days. This together with the rapid recovery observed in patients on maintenance therapy might suggest a tendency to develop a tolerance to the drug over a period of time. The fact that our several long term patients have not required increasing doses would not, however, support such a view.

Maintenance therapy. In the 123 patients receiving the drug continuously the original prothrombin varied between 66 and 138 per cent (two stage) the average being 96. The prothrombin dropped rapidly, and in most cases uniformly, to the therapeutic bracket of 10 to 30 per cent. This was achieved in from 36 to 60 hours in most instances, an occasional patient requiring less time and a few resistant cases a longer period. In the early part of the study we warily withdrew the drug when the prothrombin dropped to less than 20 per cent. In the day or two following such withdrawal the prothrombin rose to clotting levels and, despite the reinstitution of the drug, varied between levels above and below the upper therapeutic limit for some days before leveling off. It was found that this could be prevented in most instances by reducing the dosage of tromexan rather than withdrawing it entirely when the prothrombin reached therapeutic levels. Such procedure

has been entirely safe in our experience. Undoubtedly the availability of both tests has added to the safety of such procedure. Because of the relatively rapid induction and recovery periods characteristic of tromexan, some patients could not be stabilized on single daily doses. With 1 exception they were brought within the therapeutic bracket by giving the drug morning and evening. The 1 patient was at some distance from the laboratory and bloods were not available as often as was necessary.

The recovery period in most instances was between 48 and 72 hours, with a few patients requiring shorter or longer periods. Within 24 hours of the withdrawal of the drug the prothrombin had returned to levels well above the therapeutic range. Water-soluble vitamin K preparations were effective in accelerating this return toward normal in the 3 instances in which they were used. In 1 instance in which hematuria occurred the prothrombin rose from less than 1 per cent (17 per cent one stage) to 35 per cent (48 per cent one stage) 9 hours after the administration of 72 milligrams of hykinone intravenously.

The average routine for the administration of the tromexan was as follows: After the original prothrombin determinations had been made 1,800 milligrams of tromexan were given in all cases in which the level was found to be between 80 and 110 per cent. In the few instances in which it was above 110 the dose was increased to 1,950 or 2,100 milligrams. In patients having a 60 to 80 per cent level, 1,500 milligrams were given originally. If on the second day the prothrombin level (taken as a rule about 16 hours after the original dose) was 45 to 70 per cent 1,200 milligrams were given. When it remained above 70 per cent by both tests 1,500 milligrams were given. The dose on the third day was predicated entirely on the prothrombin level but was usually 900 milligrams. Most patients were controlled by this time, and the maintenance dose could usually be determined by the end of the first week. If the prothrombin varied despite continuous daily doses determinations made twice a day often showed appreciable variations and the institution of morning and evening doses served to correct this variation.

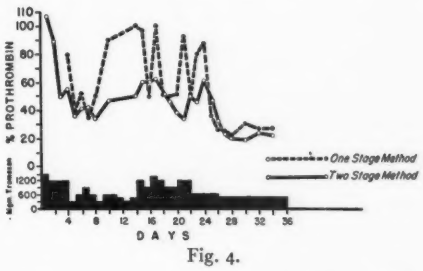

Fig. 4.

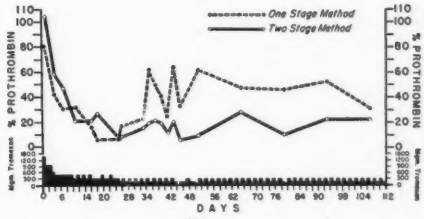

Fig. 5.

Figs. 4 and 5. The two charts shown above represent the course of patients on maintenance therapy whose prothrombin levels showed important variations as measured by the two prothrombin methods. Such variations were present in about 50 per cent of the patients on tromexan therapy. They seemed to be aggravated by a fluctuating prothrombin. Note that in Figure 4 the two methods corresponded more readily when the prothrombin had leveled off and the tromexan dosage became uniform. Inasmuch as the one stage method leaves more factors uncontrolled than does the two stage the above noted behavior of the variations under different doses of tromexan may indicate an influence of the drug on coagulation factors other than prothrombin.

In a comparison of tromexan, dicumarol, and dipaxin, the induction periods of tromexan and dipaxin were similar, i.e., in the neighborhood of 40 to 60 hours. In the case of dicumarol the composite response of the 7 patients was slightly above the therapeutic level at the end of the 96 hour period during which the patients were followed.

Daily requirements. Average daily requirements varied between 150 and 900 milligrams. The numerical average of these daily averages was 440 milligrams though the actual dosages were always multiples of 75. One patient who was difficult to control and who was given tromexan only 9 days received an average daily dose of 1,700 milligrams.

THERAPEUTIC EFFECTS

The influence of tromexan on the various thromboembolic conditions was similar to that

of dicumarol. Inasmuch as heparin was used in many of the cases during the early part of the induction period the pure tromexan effect in these cases cannot be accurately evaluated. Clinically, the results were similar in the three groups, those receiving only tromexan, those receiving heparin and tromexan, and those receiving heparin and dicumarol.

COMPLICATIONS

Hemorrhage occurred in 3 patients. This was in the form of gross hematuria and at prothrombin levels of 2.2, 17, and 1.3 per cent. Two patients were allowed to recover from their prothrombinopenia spontaneously while another received hykinone intravenously. The prothrombin in the first patient rose from 2.2 to 7.3 spontaneously in 96 hours, the bleeding having ceased 24 hours earlier. The one stage levels were 9 and 11 per cent respectively. In the second case the hematuria developed at a prothrombin level of 17 per cent (20 per cent, one stage) and ceased 48 hours later when the prothrombin was 42 per cent (49 per cent, one stage). The urinary tract did not show other cause for bleeding though it cannot be definitely ruled out. Bleeding at prothrombin levels above 10 per cent is rare. The third patient had a level of 1.3 per cent (8 per cent, one stage) when the hematuria began. He had taken 750 milligrams of tromexan just before he noted the bleeding. He received 108 milligrams of hykinone intravenously and 70 milligrams intramuscularly in divided doses over a period of 48 hours and his bleeding stopped 56 hours after it appeared. The prothrombin was 36 per cent (42 per cent, one stage) when the bleeding ceased. In this patient the hematuria developed during an upper respiratory infection when the patient had been taking 20 to 30 grains of aspirin daily for several days. Inasmuch as part of the breakdown products of aspirin are dicumarol related compounds this was considered a likely factor in the development of the hypoprothrombinemia and hematuria. The increased detoxification load on the liver as a result of the infection may also have been a factor.

Dermatitis. Eight patients of the 135 receiving tromexan developed dermatitis with itching, erythema, and in some instances urticaria-like lesions. These cases were among the patients on maintenance therapy. In 2 instances the condition was generalized with fever and distressing itching. Withdrawal of the drug and administration of antihistamine drugs were followed by disappearance of the dermatitis.

COMMENT

The pharmacology of tromexan has been recorded by several investigators among them being Stirling and Hunter and Brodie and associates. It would appear that the property of early induction and early recovery, characteristic of the drug depends upon several factors, among which are its rapid and essentially complete absorption from the gastrointestinal tract as compared to the slow and sometimes incomplete absorption of dicumarol. It is less stable than dicumarol, and hence is more rapidly destroyed and excreted. The biotransformation of tromexan is rapid, averaging about 25 per cent hourly as compared to dicumarol which averages about 40 per cent each day. It is of particular interest that Hausner and his associates using radioactively labelled tromexan and dicumarol found a similar concentration of the two drugs in the various organs and body fluids for the first 24 hours, even though prothrombin levels at this point were widely variable. Also of interest and of more clinical importance are their findings of a maximum hypoprothrombinemia 19 hours following the administration of tromexan in patients with thromboembolism, as compared to 28 hours in normal controls. Inasmuch as the modified one stage method was used in their study, it would seem possible that patients with thromboembolism have: (1) a decrease in the activity of one or more of the coagulation factors and/or (2) an increase in the activity of the anticoagulation factors. The latter, of course, would seem a likely possibility as a part of the protective mechanism, stimulated by the thromboembolic phenomena. As mentioned earlier, variations between the one and two stage test in dicumarol therapy are often marked. In the case of tromexan this has been true in 51 per cent of patients. In most of our dicumarolized

patients in which the one stage and two stage tests were run in parallel acetone-dried rabbit brain was used as thromboplastin. It is our impression that there has been less variation in such patients since soluplastin has been used though in only a few patients have the two tests been run in parallel throughout. It is possible that this may be a factor in the difference between the disparities of the two drugs. That it is not the only factor is suggested by the results in a study of the new indandione, dipaxin. In our observation of 80 patients (6) who received this drug 32 per cent showed a marked variation between the prothrombin levels as measured by the one and two stage tests. Soluplastin was used throughout as the thromboplastin in the one stage method. Reasons for disparities between the two methods and advantages of each are discussed elsewhere (4, 5, 6).

It should be pointed out that the danger during anticoagulant administration is not only from that of too much bleeding. A little bleeding may be of slight consequence, but a little clotting may mean the difference between a living and a dead patient. It is, therefore, necessary that those administering tromexan be aware of the necessity of administering it at sufficiently frequent intervals to keep the prothrombin adequately depressed. The experience of many investigators has shown that it is, as a rule, rapidly eliminated and, when necessary, its effects are quickly counteracted by adequate amounts of vitamin K and related compounds. Hence the tromexan, in most instances, should not be withdrawn when the prothrombin reaches 10 to 30 per cent of normal. The dose should be reduced and daily prothrombin levels should then determine the maintenance dose. Difficulty in the regulation of tromexan therapy may be based on the failure to follow this principle. In such practice the prothrombin will not infrequently be recorded below 10 per cent particularly when the two stage test is used. The following day, however, it will, as a rule, be again within the therapeutic bracket. A patient will rarely show evidence of bleeding when his prothrombin is between 1 and 10 per cent for a day or so. This does not, of course, mean that the prothrombin should be allowed to drop below 10 per cent for any protracted period.

The development of dermatitis in a number of our patients may have been coincidental. In an early report specific mention by Burke and Wright of the absence of urticaria, rash, idiosyncrasy, or intolerance in their 112 cases would suggest that this might be the case. In a subsequent paper, Scarrone, Beck, and Wright report the occurrence of cases of dermatitis. It is then something that should be looked for and it is our impression that the drug may be a factor in such complications.

SUMMARY

1. Tromexan was administered to 135 patients and the effects of the drug observed on the prothrombin level as measured by the one and two stage prothrombin methods.

2. The induction and recovery periods are shorter than in the case of dicumarol. The induction period is similar to that of a new indandione, dipaxin, which has a longer recovery period than either tromexan or dicumarol.

3. Therapeutic prothrombin levels were readily and early attained and easily maintained for indefinite periods of time.

4. As noted in the case of other prothrombin depressants, significant variations occurred between the one and two stage prothrombin determinations and ease of control, and particularly the safety of anticoagulant therapy, is considerably increased by the availability of both tests.

5. The observed therapeutic effect on 116 patients with thromboembolic conditions was similar to that of dicumarol.

6. Bleeding occurred in the form of gross hematuria in 3 (2.4 per cent) of the 123 patients placed on maintenance therapy. It promptly stopped when the prothrombin returned to levels above the therapeutic bracket of 10 to 30 per cent.

7. In the 1 instance in which it was given, water soluble vitamin K (hykinone) appeared to accelerate the return of the prothrombin level toward normal.

8. Dermatitis in the form of erythema and in some instances generalized urticaria-like lesions was observed in 8 patients receiving

tromexan and was considered likely to be caused by the drug.

9. Toxic manifestations other than hematuria and dermatitis were not observed.

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CARCINOMA OF THE CERVIX

Use of Matched Pairs of Cases to Compare Treatment by Surgery or Radiation

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THE recent revival of interest in this country in the surgical treatment of carcinoma of the cervix uteri has raised the question of whether surgery or radiation is the better method of therapy in this disease. There is little doubt that in far advanced lesions (stages 3 or 4, League of Nations classification) surgical treatment has little or no place, since it is almost impossible surgically to eradicate the disease. Similarly in the patient who is older or who has severe intercurrent disease the major surgical procedure required may be hazardous. However, in the relatively young and healthy patient with a stage 1 or possibly a stage 2 lesion the problem is by no means settled.

In this study an effort was made to shed light on this problem by using a different and interesting method of comparison. Patients with early carcinoma of the cervix who were treated by definitive radical surgery were matched, case for case, with a similar series of patients treated at the same institution and during the same period of time by radiation. Thus careful comparison of the results and complications of treatment could be made.

METHODS

Several methods of evaluating different types of treatment are available to the investigator. First, a group of patients treated over a period of years by one method at one institution may be compared with another group treated at another institution by a different method. This is commonly done not only in carcinoma of the cervix but in other diseases as well. Valuable information has been obtained from these studies. However, two different institutions are seldom comparable as to either patient material or adjuvant treatment. Furthermore the series have to be large before any comparisons can be made.

A second method is to compare two series of cases treated consecutively at the same institution by different methods. This has the advantage that the patient material is similar and the adjuvant treatment may be the same, but it suffers from the fact that the time required to complete such a study is long unless the volume of patients is very large; also, the methods of treatment in general use may have changed by the time the study is completed. This is particularly important in carcinoma of the cervix where both surgical and radiation treatment have changed appreciably in the past few years.

A third, and in many ways ideal, method is to take alternate cases with the same stage of disease and subject them to different treatment. The main difficulty about this method is that it requires a singleness of purpose and a degree of investigational fortitude which is hard to maintain in the face of individual differences between patients.

The method of comparison by matched pairs was selected for use in this study because it offers a different approach to the problem and obviates some of the difficulties encountered with the other methods. In using this technique, 2 patients treated by different methods are matched for as many as possible of the characteristics likely to cause variation in response. This is a research method which has been used in psychologic investigations but has not frequently been applied to medical studies. By means of it some of the variables inherent in this kind of clinical study are controlled. Each pair, in effect, represents a separate experiment. Thus a smaller number of cases is needed to obtain meaningful results. For instance, with as few as 15 pairs of cases, if 9 of the patients treated by one

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TABLE I.—MATCHING OF SURGICAL AND RADIATION CASES

Pair No.	Stage of disease	Age difference, years	Difference in initial treatment date, months
1	2	3 (S)*	1
2	1	1 (R)	9
3	1	0	1
4	1	0	5
5	1	2 (R)	1
6	1	0	3
7	1	3 (S)	3
8	1 (stump)	1 (R)	3
9	1	0	4
10	1	10 (S)	7
11	1	0	2
12	1	9 (S)	4
13	1 (stump)	4 (S)	1
14	1	3 (S)	1
15	1	2 (R)	4
Average		2.5	3.3

* Letters in parentheses indicate whether the surgical (S) or radiation (R) case was the older.

method had a certain complication, as compared with 2 of those treated by the other method, this would be a statistically significant difference (p less than 0.05).

This report is concerned with 30 patients with early invasive carcinoma of the cervix and cervical stump who were treated at the Hospital of the University of Pennsylvania during the 5 year period from November 1948 through October 1953. Fifteen patients were treated primarily by surgery, and these were matched with an equal number of patients who were treated primarily by radiation treatment.

Surgical treatment consisted of a radical panhysterectomy with removal of the parametria, upper vagina, and iliac and obturator lymph nodes. Twelve patients were operated upon from an abdominal approach and 3 from a combined abdominovaginal approach. In the 15 radiation cases treatment consisted of a course of x-radiation, followed by radium application to the cervix. X-radiation was given through external portals in all 15 cases and through an additional intravaginal portal in 13.

The 15 surgical cases were first selected and each was then matched with a suitable radiation case. These radiation cases were obtained by studying the files of all patients seen at this hospital with malignant disease of the female genital tract. Enough radiation cases were available for matching, since radiation is used more frequently than surgery in the treatment of carcinoma of the cervix in this clinic.

The patients were matched for: (1) presence of invasive carcinoma of the cervix on pathologic examination; (2) stage of disease on initial examination (League of Nations classification); (3) age; (4) date of initial treatment.

Matching radiation cases were selected in the following way: If the first two criteria were fulfilled, the radiation patient was chosen whose age was nearest that of the surgical patient, provided that: (1) the dates of initial treatment (x-radiation and operation) were within 9 months of each other; (2) if the difference in ages was more than 5 years, then the surgical patient had to be older. In no instance was there more than 1 suitable radiation patient of the same age as the surgical patient or with a similar difference in age between her and the surgical patient.

Table I shows that the pairs were well matched. There was perfect matching as to the stage of the disease. The average difference in the dates of initial treatment was small (3.3 months). The surgical patients were slightly older. In 5 pairs the ages were the same; in 6 the surgical patient was older (average 5.4 years); and in 4 pairs the radiation patient was older (average 1.5 years).

The matching did not, of course, eliminate all the variables that might influence the patient's response to treatment. However, examination of the pairs of cases in relation to associated physical abnormalities, associated pelvic abnormalities, and bodily habitus indicated that the two groups were similar. These findings are summarized in Table II.

Associated physical abnormalities in the surgical patients were: hypertension uncomplicated except by cardiac enlargement in 1, uncomplicated hypertension with asymptomatic gallstone and chronic alcoholism in 1, and hypertension uncomplicated except by cardiac enlargement with a pancreatic cyst in

1 patient. Two radiated patients had uncomplicated hypertension, 1 had inactive pulmonary tuberculosis, and 1 had sarcoidosis but was considered a good surgical risk by the medical staff.

Associated pelvic abnormalities in the surgical patients consisted of myomas in 2 (both considered to be about the size of a 2½ months pregnancy), a moderate hydrosalpinx in 1, and a small ovarian cyst in 1. Among the radiated patients the abnormalities noted were myomas in 2 (1 considered to be about the size of a 4 months' pregnancy, and 1 about the size of a 2 months' pregnancy), pelvic inflammatory disease in 2, and a small hydrosalpinx in 1. In addition, 4 surgical patients and 2 radiation patients had had previous pelvic operations of which no residua were noted on examination.

There was a little difference between the two groups as far as bodily habitus was concerned in that there were 4 obese patients in the radiation group as compared with 1 in the surgical group.

TABLE II.—MATCHING OF PAIRS IN RELATION TO ASSOCIATED ABNORMALITIES

	Associated physical abnormalities	Associated pelvic abnormalities	Obesity*
Present in neither member of pair	10	7	8
Present only in surgical case	1	3	1
Present only in radiation case	2	4	4
Present in both members of pair	2	1	0
Totals	15	15	13†

*Obesity was defined as body weight 20 per cent or more in excess of the mean recommended weight for a person of medium build of her given height.

†In 2 cases there was no record of the patient's height, and therefore they could not be classified.

RESULTS

Survival. The period of follow-up was too short to draw any conclusions about the long term effectiveness of either method of treatment. However, of the patients treated surgically, 1 died of metastases at 22 months, 1 is reported living with recurrent disease at 55 months, and the 13 others are living without evidence of recurrence at an average of 26 months after operation. Of the patients treated by radiation, 1 died of recurrence at 17 months, 1 died of intercurrent disease (sarcoidosis) at 24 months, and the 13 others are living without evidence of recurrence at an average of 26 months after treatment was begun. Thus there was little difference between the two groups as far as mortality or recurrence was concerned.

Complications of treatment. Records of complications were obtained from the follow-up notes of the patients. These appeared to be adequate in every instance. Only those complications definitely ascribable to treatment were included. Those presumably due to recurrence or spread of the original disease were omitted.

A study of the incidence of early complications (within 1 month of initial treatment) in the two groups indicated: there were no complications in 7 cases and mild complications in 8 cases of the surgical group; and no complications in 9 cases, mild complications in 5 cases, and moderate complications in 1 case of the radiation group. Mild complications in the surgical patients consisted of inability to void adequately in 4 patients, asymptomatic hydronephrosis in 1, hydronephrosis with infection in 1, pelvic hematoma in 1, and cellulitis of the leg in 1. Mild complications in the radiation group consisted of diarrhea during x-ray therapy in 3 patients, nausea and vomiting during x-ray therapy in 1, and vaginitis in 1. The 1 moderate complication in this group was a hematometrium which required 2 hospital admissions for cervical dilatation.

Late complications were noted as follows: none in 13 cases, mild in 1 case, moderate in 1 case, severe in none in the surgical patients; none in 9 cases, mild in 3 cases, moderate in 2 cases, and severe in 1 case in the radiation group. In the surgical group the 1 patient with a mild complication had marked menopausal symptoms; while the patient with a moderate complication had a recurrent pyelonephritis for which readmission to hospital was required. Mild complications in the radiation group consisted of marked menopausal symptoms in 1 patient, asymptomatic hydronephrosis in 1, and persistent diarrhea in 1. Moderate complications were persistent proctitis in 1 patient and persistent cystitis in 1.

The 1 severe complication consisted of ureteric obstruction for which nephrostomy was performed.

It will be seen that by combining these data there were 4 moderate or severe complications in the radiation group as compared with 1 in the surgical group. This is a suggestive but not a statistically significant difference.

Hospital stay. An analysis was made of the number of days of hospitalization required for the initial definitive treatment of the disease. The surgical patients spent an average of 21.5 days in the hospital as compared with an average of 16.5 days for the radiation patients. However, the radiation patients spent an additional average of 36.1 days receiving x-ray therapy on an outpatient basis. Thus the total time required for the definitive treatment in the radiation group was 42.6 days or almost twice as long as that required for the surgical group. However, it is likely that the surgical patients needed a longer period of convalescence following operation than the radiation patients required after radium application, which was the concluding part of their treatment.

DISCUSSION

Validity of diagnosis. The diagnostic criteria used in these cases to determine the presence and extent of carcinoma of the cervix were the clinical staging of the disease and the pathologic examination of a cervical biopsy. These two methods have their limitations. The first is necessarily inexact, although in all instances the staging was done by an experienced clinician (and frequently by more than one observer) according to the League of Nations classification. Pathologic reports were usually confined to a statement of the presence of tumor cells and invasion. However inexact these diagnostic criteria are, they are probably the best available at the present time. That we were in fact dealing with early lesions is indicated by the observation that in no case did the removed lymph nodes show evidence of carcinoma. In two recent representative studies Gorton found positive lymph nodes in 9.8 per cent and Meigs (5), in 17.5 per cent of those patients who had stage 1 lesions.

An important question arises as to whether it is possible to foretell the future behavior of a particular carcinoma at the time of the initial examination. The difficulties of doing this are well known. Our laboratory of surgical pathology does not attempt to grade the possible degree of malignancy on the basis of a cervical biopsy; and frequently gross descriptions of the original lesion, which might have been of some help, were incomplete. However, the similarity of the subsequent clinical course in the two groups suggests that neither one had a large proportion of highly malignant lesions.

Reasons for selection of treatment. If bias had entered into the decision to use surgery, this would affect the results of treatment. Examination of Table II indicates that this decision seemed to depend on unrelated factors, since the two groups of patients were essentially similar. Four of the surgical patients were obese as opposed to only 1 of the radiation patients. This may have been a factor in deciding operability. However, it was clearly only a minor one, since all the radiation patients were reasonably good operative risks.

Effects of variations in techniques of treatment. In all the surgical cases a definitive attempt was made to carry out radical surgery for invasive carcinoma of the cervix. That the surgical techniques could not have been identical is indicated by the fact that 7 operators were concerned and that no 1 operator was responsible for more than 5 cases. The probable result of this was that the dissections were not as extensive as if one surgeon had been responsible for all the cases. Support for this belief is obtained from the fact that the average shortest length of the removed vagina in the 10 cases in which it was measured was 2.8 centimeters.

Radiation therapy was perhaps more standardized. During the period under investigation, attempts were being made to apply the radium carefully and to estimate dosage accurately. Moreover, in the majority of cases the radiation treatment was in the hands of 1 gynecologist who was particularly interested in the radiation problems involved. All these factors probably tended to improve tumor destruction and lessen complications.

The net effect of variations in technique was hat radiation treatment tended to be more early ideal than surgical treatment. If both methods were equally effective, one might ave expected that the results obtained by urgery in this series would have been worse han those obtained by radiation. This was ot the case. Survival and incidence of recurence were similar in both groups. Although he follow-up period was only for an average f 26 months, there is no reason for supposing hat the later results will differ greatly from he early ones, as Meigs (6) has suggested.

As far as complications were concerned, nore severe ones were found in the radiation atients. One reason for this was the absence f ureteral injuries in the surgical patients. 'omposite figures from three recent studies one in this country by Meigs (5), Kelso, and 'eterson and Hornbrook indicate that this najor complication has been noted in 19 or .4 per cent of 227 cases of carcinoma of the ervix treated surgically. In addition there ere no rectovaginal fistulas or vesicovaginal stulas in this series, although these have been bserved in the 3 other studies mentioned. 'erhaps the reason for absence of these unoward effects of surgery is, as Brunschwig uggests, that the operators, being relatively nexperienced, were more cautious and less adical in their dissection. At any rate the act remains that in this series surgical treatment can be said to have been as good if not better than radiation in respect to complications.

Surgery following radiation. In none of the cases in this series was radical surgery used either before or after radiation therapy. Such combinations of treatment may in some instances be necessary and beneficial. In fact, it has been stated that a particular indication for surgical treatment in carcinoma of the cervix is failure of response to radiation. Moreover, Graham has been able to predict response to radiation from serial examinations of vaginal smears: patients who are thus shown to respond poorly may then be candidates for surgery. Meigs (5), however, states that a combination of surgery and radiation is not ideal. From a theoretic standpoint it might be supposed that this is true. The response of the patient's tissues to radiation frequently results in considerable reaction in the pelvis which may impede dissection and hinder healing.

SUMMARY AND CONCLUSIONS

1. The treatment of early carcinoma of the cervix was studied using the method of matched pairs of cases. This is a different method from those commonly used in this type of investigation and offers certain definite advantages.

2. Fifteen patients with early carcinoma of the cervix who were treated primarily by radical surgery at the Hospital of the University of Pennsylvania were matched with 15 patients who were treated primarily by radiation at the same hospital over the same period of time.

3. There was little difference between the two groups over an average follow-up period of 26 months in survival, recurrence of disease, or the incidence of early or late complications of treatment.

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CONGENITAL ATRESIA OF THE COLON

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CONGENITAL atresia of the colon comprises about 5 to 10 per cent of all congenital intestinal occlusions, exclusive of anus, rectum, and esophagus. Colon atresia is not, therefore, a commonly encountered condition. However, atresia occurs somewhere in the large or small bowel in one of every 3,000 births according to Louw's recent experience. This is considerably more frequent than 1 in 20,000 as originally reported by Webb in 1931. The incidence computed by Evans, based on an exhaustive review of the world's literature, is 1 in 1,500 births. If the latter figure is subsequently shown to be the true incidence of intestinal atresia, then we face a real surgical challenge, for the mortality rate of operation for congenital intrinsic intestinal obstruction in the larger children's hospitals in the United States and England varies from 43 to 82 per cent. Since most of the births in the United States take place in hospitals which are not primarily children's medical centers, it would appear that the surgical mortality rate for congenital atresia that obtains for the entire country must be appallingly high—only an occasional infant with this anomaly survives. Evans could find only 139 recorded survivals in the world's literature. To express the challenge in another way, it is likely that the number of babies with atresia who are surgical failures or who fail to come to surgery is about 2,200 annually in the United States.[1] This same number of persons (through 55 years of age) died from appendicitis in the United States during the year 1949. Approximately the same number of individuals of all ages died of rheumatic fever during that year. When the mortality of intestinal atresia is compared with the mortality of these common illnesses which are widely recognized as public health problems, it becomes apparent that there is a need for emphasis on the diagnosis and improved management of newborn infants with atresia of the gut.

This review of the subject of colon atresia and the accompanying case report serve to emphasize some of the problems in management and surgical judgment that are common to many of the congenital intestinal occlusions. That no adequate solution to these problems exists at the present time is attested to by the fact that only 6 individuals have been reported heretofore as having survived operation for complete obstruction of the colon due to atresia. A summary of these case reports and of the 1 reported in this communication appears in Table I.

The following case report is submitted to illustrate the fate of the miniature colon beyond a point of atresia after bowel continuity was established. This is the first survivor of multiple colon atresia to be recorded. The report has an additional point of interest in that the complication of gangrenous ileum attending a midgut volvulus made necessary an extensive resection of large and small bowel which was followed by immediate anastomosis. We have found no record of a comparable surgical procedure with recovery in a 36 hour old infant.

V.M., Parkland Hospital, 91923. A full term white female infant was delivered without complication by low forceps on December 2, 1951; she breathed and cried spontaneously and no abnormalities were noted by the obstetrician. Birth weight was 5 pounds, 10 ounces. The first few feedings were taken without difficulty, but after the subsequent feedings the infant vomited bile stained liquid and 30 hours after birth her abdomen was distended. Bowel movements had not occurred. Rectal examination revealed no obstruction to the examining finger, and there was no meconium present in the rectum. A mucus plug was extruded following the examination and the Farber test performed on this material was negative. Diodrast was instilled into the rectum but could not be forced beyond the beginning of the sigmoid colon (Fig. 1). Roentgenograms in the anteroposterior projection of the abdomen were obtained with the infant horizontal and

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[1]This figure is based on the present birth rate in the U. S. and on an 80 per cent operative mortality rate which probably is lower than that which actually exists. Evans' estimate of frequency of atresia was used.

TABLE 1.—SURVIVALS FOLLOWING SURGERY FOR CONGENITAL ATRESIA OF THE COLON WITH COMPLETE OBSTRUCTION*

Author and year	Age at operation	Sex	Site of colon obstruction	Attendant abnormalities	Treatment	Remarks
Gaub 1922	33 hours	M	Sigmoid	None	Colostomy (left lower quadrant)	Three year observation. Normal development. No attempt to close colostomy
Potts 1947	3 days	F	Transverse	None	Side-to-side anastomosis of transverse colon around atretic site	Barium enema on 19th postoperative day revealed enlargement of lumen. No follow-up reported
Lemon and Walker 1948	1 hour	M	One long atretic segment from cecum to splenic flexure	Congenital evisceration. Failure of bowel rotation. Premature (4 lbs. 3 oz.)	Side-to-side ileocolostomy. Through-and-through closure of abdominal wall	At 9 months the baby weighed 16.5 pounds
Lee and MacMillan 1950	3 days	M	Transverse	Perforation of cecum	Closure of cecal perforation at age 2.5 days; then at second operation resection of atresia and cuff of distended bowel and side-to-side anastomosis	At 2 months a cecostomy was done for obstruction at site of anastomosis then resection of narrowed segment and anastomosis. At 4 months weighed 15 pounds but still distended proximal colon
Jemson 1951	3 days	F	Ascending	None	Side-to-side anastomosis	At 6 months the baby was in "excellent health"
Gann and Hoffman 1952	2.5 days	Not given	Sigmoid	None	Side-to-side anastomosis	No follow-up reported
Wilson, Nelson, Harshbarger 1953	36 hours	F	1) Cecum 2) Transverse	Fetal peritonitis. Midgut volvulus. Failure mesenteric fixation. Universal mesentery. Gangrene 35 cm. of ileum and cecum	Primary resection of gangrenous ileum and of cecum, ascending and transverse colon; with end-to-side anastomosis of ileum to sigmoid	At 1.5 years normal mental and physical development. Normal bowel movements (Fig. 5)

*No follow-up after discharge from the hospital was given in 2 of the reports (Cases 2 and 4), and the eventual outcome is not known; however, these are listed as survivors. No cases are included in which the obstruction of the colon was incomplete. There are reports of older children and adults who have had surgical correction of congenital colonic stenosis, but these cases are not germane to the problem of management of atresia in the newborn. Gross indicates in his textbook that there have been 2 survivors of colon atresia from Boston Children's Hospital; but since no data are available regarding these patients they are not included in this table.

ith the head tilted down. The films revealed gas patterns which were interpreted as being due to an atresia of the distal one-half of the colon and a coexisting midgut volvulus. A nasogastric tube was placed and the stomach emptied. Fifty milliliters of dextrose-amigen-Ringer's solution were given by clysis and a cannula was placed in a saphenous vein through which lactate-Ringer's solution was infused. The hemoglobin concentration was 17.3 grams per cent; the white blood cell count was 17,600 and the differential count revealed 62 neutrophilic segmented cells, 6 band cells, and 32 lymphocytes.

Thirty-six hours after birth, the baby was anesthetized with cyclopropane through a to-and-fro breathing circuit. The abdomen was entered through a long vertical left rectus incision; the rectus muscle was retracted laterally. There was a moderate amount of blood-tinged fluid in the peritoneal cavity. Many tremendously dilated loops of small bowel presented in the wound; these loops were intensely cyanotic. There was evidence that fetal peritonitis had existed in that there were many adhesions between loops of bowel and between bowel and parietal peritoneum. All the small bowel was delivered through the incision and a counterclockwise volvulus of 360 degrees of the entire midgut was identified. The volvulus was reduced and it was seen that the entire bowel was suspended from a common mesentery which had only one short segment of posterior attachment through which the mesenteric vessels coursed. The distal two-thirds of the ileum was gangrenous. The ileocecal junction was identified only by the presence of the appendix. The cecum was immediately under the liver, and this segment of gut was gangrenous. There was a point of atresia immediately distal to the cecum. The remainder of the colon was uniformly about 5 millimeters in diameter, but it contained a lumen as proved by the injection of air. The bowel appeared normal except for its miniature size and its relative lack of distensibility. However, in the midtransverse colon another atretic segment completely obstructed the flow of air even though the external appearance of the bowel was not altered at this point and the mesentery was continuous (Fig. 2). Consequently about 35 centimeters of distal gangrenous ileum, the cecum, and colon were resected to the splenic flexure. The proximal portion of the descending colon could not be visualized because of dense adhesions in the left upper abdominal quadrant and its patency could not unequivocally be established at that time; therefore, the colon was closed immediately proximal to the splenic flexure and an anastomosis of the end of ileum to the side of sigmoid was performed (Fig. 3)

Fig. 1. The diodrast enema reveals a normal rectal ampulla with obstruction to the contrast medium in the sigmoid. The gas filled loop in the right side of the abdomen was interpreted as being cecum, ascending colon, and hepatic flexure with complete obstruction in the transverse colon. Actually the massively dilated loop was found at operation to be gangrenous terminal ileum. The atresia existed just distal to the head of the cecum which lay in the right upper quadrant. The cluster of gaseous shadows contained in uniformly dilated small bowel in the left side of the abdomen is roentgenographically characteristic of midgut volvulus which this proved to be.

since patency of the sigmoid colon to the anus was assured by the fact that air injected into the sigmoid escaped from the anus. The anastomosis was technically difficult in that the ileum was approximately 2.5 centimeters in diameter and the sigmoid colon was about 5 millimeters in diameter. Air was injected into the colon in an attempt to overcome the disparity in size but this was of little help. The two layered anastomosis was completed, tested, and found to be patent and the abdomen was closed in layers. During the operative procedure which required 2½ hours, the patient was given 100 milliliters of whole blood and 250 milliliters of lactate-Ringer's solution intravenously. Subsequent examination of the resected bowel revealed a 35 centimeter segment of gangrenous small bowel and one point of atresia at the cecum just distal to the ileocolic junction; the latter was identified by the position of the appendix. The remainder of the colon had a lumen except in its mid-transverse portion where a complete diaphragm was found; the lumen continued beyond this point to the transected end.

Postoperatively, audible peristaltic activity was present and meconium stools were passed within 36 hours, but the baby vomited when gastric suction was discontinued so it was necessary to maintain Wangensteen suction for 4 days. Penicillin was the only antibiotic given during this time; streptomycin was given subsequently for 3 days. Parenteral fluids were given exclusively during the first 4 days and were given as a supplement to the oral intake for 2 additional days. The infant was given a boiled skimmed milk formula and later a lactic acid milk formula, and she slowly gained weight.

Excoriation of the buttocks was severe soon after operation as the result of many loose stools which had a pH higher than 8. Pyruvic acid in starch paste was applied to the perianal skin and the irritation ceased. The infant was discharged from the hospital on the eighteenth postoperative day. At that time she was having 6 to 8 soft stools a day. She had regained her birth weight and was taking her formula well. One or 2 feedings of lactic acid milk were given each day, because if these feedings were omitted excoriation of the buttocks had a tendency to recur.

Eight months later she was admitted to the hospital for the investigation of an anemia which was corrected dramatically by the administration of iron. At that time she weighed 15 pounds, 4 ounces, and appeared in good health. A barium enema was done and revealed that the ileocolic anastomosis was of adequate caliber and that the lumen of the descending colon and sigmoid colon had increased to approximately normal size.

She was seen again for routine examination on April 7, 1953 and she weighed 22½ pounds. She was having 1 to 2 formed bowel movements daily. Another barium enema was done on May 29, 1953 and revealed an elongated sigmoid (Fig. 4). Physical development and accomplishments were completely normal (Fig. 5).

DISCUSSION

From a study of the reports of infants with colon atresia who died and of the few who survived, it appears that two factors are eminent in their contributions to the currently high death rate: (1) the delay in definitive treatment which arises from the physician's inability to recognize intestinal obstruction without repeated and time-consuming diagnostic studies and his unwillingness to accept the urgency of the need for surgical treatment of this condition in the newborn; and (2) the inadequate surgery which is performed as a result of the surgeon's premise that minimal abdominal exploration and the "least shocking" procedure to relieve the obstruction are all that is required to rectify the mistakes of nature.

What are the consequences of delay?

In all cases of gut atresia the mortality of operation rises linearly with the age of the patient and approaches 100 per cent at an average age of 5.8 days. All of the successfully treated patients with colon atresia were operated on during the first 3 days of life; but still of the survivors were found at operation at 36 and 60 hours, respectively, to have gangrenous or perforated bowel as a result of the obstruction or an accompanying volvulus. The development of necrosis of bowel in the first 48 hours of life has also been observed by Ladd, Sweet, and Moses. In Louw's cases of all types of intestinal atresia, frank perforation or gangrene occurred in 23 per cent. Contrary to what one might anticipate one-fourth of those complicated cases came to operation within 48 hours of birth. It is apparent that one cannot predict on a basis of age whether the complications of gangrene or perforation of bowel have supervened in a given individual with atresia. In other words, there is no safe period during which procrastination is beneficial, nor is there a subsequent golden hour when the infants tolerate surgery better. It follows then, that operation should be performed soon after the diagnosis of atresia has been made and if surgery is to be successful, the diagnosis must be made relatively soon after birth.

What are the consequences of inadequate surgery?

Inadequate surgery was found to be due to (1) incomplete exploration, or (2) the failure to perform definitive procedures.

Incomplete exploration. Associated congenital anomalies of the digestive system occur more commonly with atresia of the colon than with occlusions elsewhere in the intestinal tract. Of those infants listed in the literature who died with colon atresia, many had associated abnormalities, and in Louw's consecutive series of 7 nonsurvivors, 6 were afflicted with additional developmental errors. Of the 7 babies who have survived surgery, only 2 had multiple anomalies, all of which were confined to the abdominal wall or the abdominal contents (Table I). Some of the deaths following surgery for colon atresia were due to undiscovered second or third lesions after only 1 lesion had been surgically corrected. Moore recently described such a case, and in fact this sequence of events was lamented in many of the case reports that were reviewed. The philosophy of doing the least possible to these sick infants cannot be condoned when

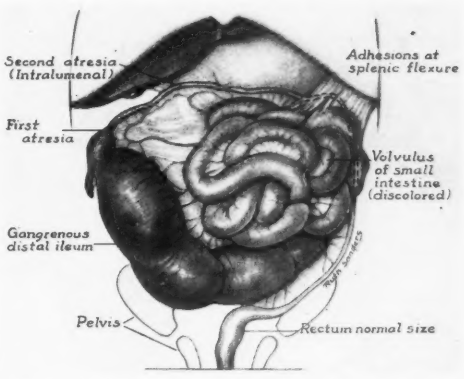

Fig. 2. This is a schematic illustration of the midgut volvulus, gangrenous ileum, 2 sites of colon atresia, and the small distal colon that were encountered at operation in the 36 hour old infant reported herein. The rectal ampulla was of normal size. There were many firm old adhesions between all loops of small bowel which indicated the previous existence of peritonitis.

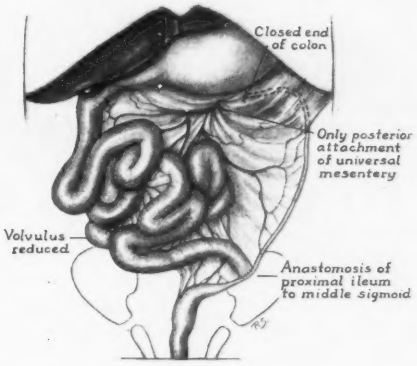
Closed end of colon
Only posterior attachment of universal mesentery
Volvulus reduced
Anastomosis of proximal ileum to middle sigmoid

Fig. 3. This illustration schematically represents the intestinal continuity after reduction of the volvulus and resection of 35 centimeters of gangrenous ileum, cecum, and colon to the splenic flexure. The colon was closed at the splenic flexure since the adhesions were so dense in this area that further resection was impossible and lumen patency could not be established. Consequently the end-to-side anastomosis was made between proximal ileum and sigmoid colon where patency of the lumen was assured by air injection.

one considers that the intestinal occlusions are multiple in 16 to 25 per cent of the babies and as many as 90 per cent of those with colon atresia have coexisting anomalies of abdominal contents or parietes, some of which are incompatible with life. The corollary to be derived is that a complete abdominal exploration must be performed, rather than a limited one. Determination of the patency of the lumen distal to the atresia by the injection of air into the bowel is essential in order to discover additional obstructive lesions.

Volvulus is a complication that accompanies atresia of the bowel in about one-third of the cases; among the survivors of colon atresia, volvulus was seen once (our Case, 7, Table I). The frequent coincidence of these two conditions should be expected in that nearly one-half of the infants with atresia also have deficient mesenteric fixation which predisposes to volvulus. The common coexistence of volvulus with atresia speaks for the necessity of thorough abdominal exploration in the newborn when operation is being performed for intestinal obstruction because volvulus is often impossible to recognize until the entire midgut is delivered through the abdominal incision.

Failure to perform definitive surgery. Congenital microcolon was listed as an associated anomaly or as the primary cause of obstruction in many of the recorded cases. It is likely, however, that congenital microcolon does not exist as an entity, since all of the reported instances have been attended by obstruction of the bowel proximal to the microcolon. Microcolon then is not a developmental error but rather an undilated and excluded colon, the presence of which is pathognomonic evidence that an obstruction exists at some proximal point. If this attitude toward microcolon had been generally adopted by surgeons, the number of recorded survivors might be greater. Instead microcolon is usually regarded as an interesting and rare curiosity with which no individual has yet survived,[1] so when a colon 5 millimeters in diameter is seen during abdominal exploration in a newborn infant, the abdomen is frequently closed without any attempt being made to relieve the obstruction. Death inevitably follows an unrelieved obstruction or an obstruction of the colon that is relieved only by an ileostomy[2]. In fact we have found no reported cases of atresia of the right or transverse colon that have survived following proximal colostomy. The only infant to survive proximal colostomy had a low sigmoid atresia and the proximal sigmoid was exteriorized (Table I). *Definitive surgery of colon atresia must include relief of the obstruction and the restoration of continuity of functional bowel.*

In congenital atresia of the colon, functional continuity of the bowel is not always restored even though an anastomosis has been done and anatomic patency of the lumen has been established. Several deterrents to the passage of intestinal content may persist after a technically perfect anastomosis has been effected, for example a long distal segment of an undilated colon, despite lumen patency, does not propel feces at a rate comparable to normal bowel. Time is required for this tiny colon to dilate and to become functionally normal; until it gains this ability a functional obstruction exists and the integrity of a recent anastomosis is thereby jeopardized. Consequently, the anastomosis around an atretic segment of colon should be made into descending colon or at least left transverse colon in order to minimize the length of miniature colon through which intestinal contents must pass. In Table I it can be seen that all of the successful anastomoses, save one,[3] have been made into distal colon. The theoretic disadvantage that persistent diarrhea may follow ileodescending colostomy did not obtain in our case. Apparently the cul-de-sac colon loop between the closure at the splenic flexure and the anastomosis at the sigmoid has functioned as a colonic reservoir. In Figure 4 this reservoir and the (compensatory?) elongation of the sigmoid colon can be seen. Since the reservoir loop is

[1]The colon which lay beyond the cecal obstruction in the successfully treated infant reported herein satisfies the description and definition of congenital microcolon as originally formulated by Greig.

[2]Evans has employed enterostomy successfully in 3 cases of small bowel atresia. The enterostomy was used as the first part of a planned two stage procedure with restoration of bowel continuity 2 to 3 days later.

[3]The site of anastomosis in Jemson's case is not described. Severe abdominal distention protracted the postoperative recovery period and liquid paraffin enemas injected with pressure were used to dilate the distal colon.

Fig. 4.

Fig. 5.

Fig. 4. This barium enema was performed when the child was 1.5 years of age and demonstrates approximately normal caliber of the remaining colon, but considerable elongation of the sigmoid has occurred. The end-to-side anastomosis of ileum to sigmoid now lies in the right side of the abdomen. The anastomotic opening is of adequate size and there is no small bowel distention. The reservoir colon loop between the anastomosis and the site of closure at the splenic flexure filled and emptied readily.

Fig. 5. This photograph shows the appearance of the child at the age of 1.5 years. Mental and physical development have been normal. She has 1 to 2 formed bowel movements daily.

isoperistaltic it tends to empty well; consequently we do not anticipate the development of the refractory anemia that occurs in some individuals who have a surgically created blind loop of bowel with peristaltic orientation which does not favor emptying of the loop.

Following a successful anastomosis for atresia, functional bowel continuity may not be established because the excessively stretched smooth muscle of the distended proximal gut is often decompensated. As a consequence, ileus persists in the postoperative period and impairs anastomotic healing. That imperfect healing of the anastomosis is a fundamental problem in the salvage of these babies is emphasized by the fact that one of the major causes of death following surgery for atresia of the bowel is leakage from the anastomosis with development of peritonitis. Resection of the severely distended and friable bowel immediately proximal to the obstructed segment tends to obviate this danger that often follows a short circuiting anastomosis without resection since the anastomosis after resection can be performed by using gut which is not friable and which is capable of effective peristaltic activity. Furthermore, resection of the obstructed segment and a generous length of proximal bowel will likely prevent some of the late deaths (5 to 8 weeks after simple anastomosis) that have been noted by many students of neonatal intestinal obstruction. Characteristically, the anastomosis is found to be patent at autopsy but the afferent limb of the anastomosis is still dilated. The bowel proximal to the atresia, in these instances, is inimical to the recovery of normal intestinal motor function despite circumvention of the lumen

occlusion. Perhaps the failure of the afferent loop to recover functionally is due to an irreversible decompensation of smooth muscle, or it may be due to an absence of myenteric plexus ganglion cells as described by Zuelzer and Wilson. In either event this proximal segment of defective gut should be removed at the primary operation.

A limited resection of a cuff of bowel adjacent to an atresia in the transverse colon of one baby (Case 4, see Table I) was successful in that the infant lived, but distention of the proximal colon and obstructive signs persisted. Two months later operation had to be performed and, again, a limited resection with anastomosis was performed. At 4 months of age distention of the proximal colon still was present. Likely resection of the entire proximal colon will have to be done before the symptoms of obstruction completely abate.

These considerations indicating the superiority of resection and anastomosis over anastomosis without resection are validated in fact by the experiences reported by Louw in which the mortality of resection and primary anastomosis for jejunoileal atresia was 25 per cent while anastomotic procedures alone were attended by a 90 per cent mortality.

It is recognized that definitive surgery cannot be performed with an acceptable incidence of survival without highly skilled anesthetists who are familiar with the physiologic peculiarities of the newborn in illness. We are also cognizant that the supportive care of the infant in large part determines survival, for example: emptying the stomach and maintaining gastric suction prior to anesthesia, during, and after surgery; the intelligent replacement of salt solutions by signs of need and evidence of loss rather than by inflexible formulas and rote; the replacement of water at rates comparable to urinary and insensible losses; the restraint from routine administration of whole blood when no circulating red cell deficit exists prior to surgery in an effort to "prevent" shock, especially when the hemoglobin concentration is high and extracellular fluid losses have been great; the infusion of whole blood during surgery should significant losses of blood occur; and close postoperative scrutiny to prevent, detect, and treat pulmonary atelectasis and pneumonia, gastric dilatation, intestinal distention, water and salt deficits and excesses, and nutritional needs.

SUMMARY

1. A review of the literature reveals only 6 previous survivors of surgery for congenital atresia of the colon. We are reporting the first survivor of multiple colon atresia; this case was further complicated by midgut volvulus and gangrene of the ileum.

2. Some of the factors contributing to the high mortality in congenital atresia of the colon are discussed.

3. Definitive surgical treatment of atresia is urged rather than palliative procedures designed only to relieve the immediate obstruction of the lumen. Surgery should be performed soon after the diagnosis of colon atresia is established and should consist of: (a) thorough abdominal exploration; (b) determination of lumen patency beyond the point of atresia; (c) resection of the atretic bowel and the segment of severely distended proximal (large and small) bowel; (d) the performance of primary anastomosis into the descending colon; and (e) a reservoir colon loop should be left proximal to the anastomosis, if possible. Proximal colostomy is not preferred except for left colon atresia in an infant that is severely ill.

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ABDOMINAL WOUND DISRUPTION

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IT IS difficult to consider the question of abdominal wound disruption without reviewing briefly some factors which influence the healing process. In order to prevent this complication the surgeon must possess an intimate knowledge of wound healing. It should be realized, however, that no single factor is responsible for wound disruption and in any one case several agents may combine to cause the wound breakdown.

Arey has reviewed the general principles of wound healing and has pointed out that it is influenced by a number of variables including age, temperature, and nutrition. The healing process in a young individual is more rapid than in older persons, and consequently wound breakdown is more common with advancing age. While a rise in temperature increases the rate of healing the clinical application of this is relatively unimportant.

The factors of age and temperature are impossible to control. Nutritional factors on the other hand can be regulated to some extent both in the preoperative and postoperative periods.

Poorly nourished patients are often subject to delay in or failure of healing. Working on the tensile strength of incised wounds Harvey and Howes showed that the latent period is normally 4 days and thereafter healing becomes apparent with multiplication and maturation of fibroblasts and intercellular substances. During the latent period the wound strength is solely dependent upon the sutures used. As the latent period ends fibroplasia begins and the velocity of growth is thereafter constant and progressively diminishes after maximum wound strength is obtained. These workers were able to show that a high protein diet, while having no effect upon the lag period, gave a marked increase in the development of tensile strength in the ensuing days and that the time to reach maximum tensile strength was decreased. In protein deficient animals, abdominal incisions heal poorly, frequently disrupt, and show a marked intercellular edema and delay in fibroblastic proliferation. It has been suggested that the relationship of hypoproteinemia to wound healing is mainly on an osmotic basis. Recently Kobak measured the tensile strength of abdominal wounds in rats and noted a difference in the latent period between the controls and the protein deficient animals. The lowered tensile strength in the latter is apparently due to a diminution in the number of fibroblasts, a decrease in their rate of maturation and a delay in the maturation of the reticulum into mature collagen. dl-Methionine may be the protein fraction which causes this upset in wound healing and its use may prevent this complication. Clinically it has been found that a significant percentage of patients with wound disruption have a low plasma protein level and particularly a low serum albumen. It has also been shown in other patients whose wounds have disrupted that although the serum protein concentrations are normal, the tissue protein level, particularly in the fascia, is low.

TABLE I.—INCIDENCE RELATED TO PROCEDURE

Operation	No. of operations	No. of disruptions	Incidence per cent
Stomach	2,242	25	1.1
Biliary tract	2,738	15	0.55
Small bowel	517	5	0.97
Large bowel	1,305	13	1.0
Appendectomy	7,517	5	0.07
Laparotomy	1,392	13	0.94
Gynecologic	5,166	37	0.71
Cesarean section	1,434	2	0.14
Totals	22,311	113	0.51

Ascorbic acid deficiency causes an inhibition of fibroplasia and collagen formation and also such intracellular substance as is present is poorly maintained. There is a marked decrease in the strength of wounds in vitamin C deficient animals and such animals appear to be more susceptible to wound infection. The tensile strength in these animals is less than that of the control group. However, it is possible that there may be a selective concentration of ascorbic acid in a wounded part even if the general level is low.

It has been shown experimentally that pyridoxine and riboflavin deficiencies will delay healing of surface wounds although this has not been substantiated in human subjects.

Much work has been done in an attempt to show the influence of various types of suture material. Madsen has pointed out that the ideal suture must satisfy three criteria: (a) it must tie securely so that the knot will not slip under strain; (b) it must be sufficiently strong to withstand the tension which occurs within the first 10 to 14 days after operation when the whole strength of the wound is dependent upon the sutures; and (c) it should not cause such a reaction in the tissues that the healing process is retarded or the suture itself disintegrates prematurely.

The most commonly employed material is catgut but this has several disadvantages. The tensile strength of catgut decreases rapidly when introduced into a wound especially if there is an accumulation of serum or if there is inflammatory exudate present. It has also been shown that guinea pigs may be sensitized to catgut which, if reintroduced into the same animal, causes a marked local reaction resulting in rapid absorption of the suture material. If this work is substantiated in humans it might account for a failure in wound healing in patients who have had two operations in which catgut has been used. The nonabsorbable sutures—silk, cotton, and wire—offer the least tissue reaction, the greatest tensile strength, and the greatest security. The use of fine sutures, the avoidance of mass ligation of tissue, and the exact coaptation of the fascial and peritoneal layers are of much more importance than the suture material which is used.

It is generally agreed that the vertical incision, particularly that in the upper abdomen, is most prone to disruption. The transverse incision tends to preserve the nerve and blood supply to the muscle layer and, of more importance, preserves the integrity of the transversalis muscle. When this muscle is divided vertically it tends to pull the peritoneal layer apart allowing a small piece of omentum or bowel to protrude, which is often the initial step in wound disruption.

Widely divergent experimental evidence is reported as to the effect of ACTH and cortisone in wound healing. In animals receiving cortisone there is an impairment in healing associated with a delay in the appearance of connective tissue in the wounds. However, in spite of this histologic evidence, the results in humans do not substantiate this finding and healing appears to progress normally except in those patients who have been on therapy for a long period of time before operation. In these patients there appears to be an impairment in the healing process.

During recent years the interest in early ambulation has led several workers to assess its relation to the healing of abdominal wounds. Comparing the tensile strength of abdominal wounds in dogs exercised daily with a similar group kept closely confined, Royster showed that the tensile strength of the wounds in exercised dogs did not differ from the controls. Certainly from a clinical viewpoint early ambulation of patients does not appear to have affected the incidence of wound disruption.

MATERIAL

A study was made of the case records of 113 bdominal wound disruptions occurring on he General Surgical Service and the Obstetri- al and Gynecological Services of the Royal 'ictoria Hospital in the 12 year period from 941 to 1952. During this time 22,311 major bdominal operations were performed, giving n overall incidence of wound disruption of .51 per cent. The incidence of this complica- ion on the General Surgical Service was 0.47 er cent in 15,711 abdominal procedures, while n the Obstetrical and Gynecological Services ne incidence was 0.59 per cent in 1,434 esarean sections and 5,166 gynecologic rocedures. The overall ratio of wound dis- uption in males to females is 2.6 to 1, but on ne General Surgical Service alone, which is robably a more accurate comparison, this atio was 6.7 to 1.

A comparison was made between the inci- ence of disruption and the type of operation Table I). It is not apparent why operations n the biliary tract compare favorably in spect to this complication with other upper bdominal operations of similar degree. Note- worthy also is the low incidence of disruption ollowing cesarean section, it being only one- fth as frequent as in comparable gynecologic rocedures, in which similar incisions, suture naterials, and techniques of closure are used. The lower average age of obstetric patients, the good vascularity of the tissues, and the relaxed abdominal wall in the postoperative phase are contributing factors.

Relating operating time to this complication (and considering time of operation as some indication of its difficulty) it was found that 24 per cent of disruptions occurred following operations of less than 1 hour, 43 per cent following procedures of 1 to 2 hours and the remaining 33 per cent following lengthy and often difficult procedures of over 2 hours' duration. Of the wounds which disrupted, 80 per cent of the primary operations were per- formed by the attending staff, but this does not imply that an equivalent percentage of wounds were closed by the operating surgeon, as it is customary on many services for the first assistant to complete the closure of the wound.

TABLE II.—DISRUPTION RELATED TO INCISION

Site of incision	No. of operations	No. of disruptions	Incidence per cent
Upper abdominal	6,588	62	0.94
Lower abdominal	9,420	51	0.54
Midline incisions	7,480	54	0.72
Upper midline	1,020	15	1.46
Lower midline	6,460	39	0.60
Other than midline	8,528	59	0.69

McBurney incisions are excluded from above.

Wound disruption is related to the type of incision used in the primary operation (Table II). Our findings are in agreement with others, in that upper abdominal incisions are more prone to disruption than are those in the lower abdomen. The same applies to midline incisions despite the fact that they are used almost exclusively for gastric and pelvic surgery often of an elective nature. It should also be noted that many midline skin incisions penetrate the fascia lateral to the midline and are paramedian in respect to this layer, al- though included in the midline category. All of the lower midline disruptions occurred fol- lowing gynecologic procedures or cesarean sections, this incision, with few exceptions, being used routinely for pelvic surgery. No McBurney incisions disrupted, although this was the incision of choice in over 7,500 ap- pendectomies done during the period of study. This large group was, therefore, excluded in comparing incision sites with one another, as it would markedly alter the results obtained. There were 4 disruptions in upper abdominal transverse or paracostal incisions but these incisions were not used extensively.

The suture material used in the closure of those wounds which subsequently disrupted is listed in Table III. It was not possible accu- rately to assess the relative frequency of dis- ruption in respect to each type or combination of suture material. Catgut continues to be used in the majority of closures, and there is no evidence to suggest that the incidence of disruption in such cases is proportionately higher. In the combined usage of catgut with silk or wire, the former was usually used to close the peritoneum, while the silk or wire was used for the fascial layers.

TABLE III.—CLOSURE MATERIAL USED IN 113 DISRUPTIONS

Suture material	No. of cases	Per cent
Catgut	77	68.2
Catgut and silk	7	6.2
Catgut and wire	16	14.1
Silk	6	5.3
Wire	7	6.2

An effort was made to compare catgut with wire, the latter being used routinely on one service during the 5 year period from 1948 to 1952 (Table IV). Appendectomies and obstetric and gynecologic operations have been excluded from this table as wire closure has rarely been used in these cases.

In a small percentage of those patients whose wounds disrupted following wire closure, it appears that wire was selected as a closure material because the increased likelihood of this complication was recognized at the time of operation.

In respect to closure technique, continuous closure of the main fascial layer was used in one-third of the 113 disruptions, while interrupted sutures were used in the remaining two-thirds. Again, these figures have no value unless the relative frequency of each type of closure is accurately known. Tension sutures were used in 39 per cent of cases in which disruption subsequently occurred, and no definite conclusions could be reached as to their value as a prophylactic measure.

With respect to time of wound breakdown, it was found that 24 per cent of disruptions occurred during the first 5 days after operation, 55 per cent occurred 6 to 9 days inclusive, and the remaining 21 per cent on or after the tenth day. The time of disruption was taken as the time it was first discovered through separated skin edges. In many cases it would appear that separation of the deeper tissues took place some time before the skin, which remained intact until removal of clips or superficial sutures. Copious serosanguineous discharge preceded wound disruption in 44 per cent of the cases studied.

TABLE IV.—COMPARISON OF WIRE AND CATGUT (1948 to 1952)

Suture material	No. of cases	No. of disruptions	Incidence per cent
Wire	1,728	15	0.86
Catgut	1,925	15	0.78

Appendectomies and gynecologic operations are excluded from above.

In respect to degree of disruption during the period of study all cases were included in which the complication was of sufficient degree that secondary suture in the operating room under general anesthesia was performed. Eighty-five per cent of those reported were complete, involving all layers, 7 per cent involved all layers except the peritoneum, and the remaining 8 per cent involved only skin and subcutaneous tissue.

In an effort to evaluate different etiologic factors in wound disruption, important associated conditions in the 113 cases under study were tabulated (Table V). The triad of cough, vomiting, and distention are considered together, as they have the common effect of increasing tension in the healing abdominal wall, either spasmodically as in cough and vomiting, or continuously, as in distention. It is significant that 75 per cent of patients studied exhibited these symptoms, either singly or in combination, to an excessive degree. These mechanical factors are, therefore, considered to be of prime importance in the etiology.

While 35 per cent of patients had a febrile course postoperatively, gross wound infection was apparent in only 13 per cent of the open wounds. As two-thirds of the patients had antibiotics administered following the primary procedure, and usually started within 48 hours, it is difficult to attribute any but a minor etiologic role to infection.

In many cases in which cancer was involved, extensive operations were performed on patients who showed weight loss, anemia, and sometimes altered protein levels in the preoperative phase. While one-third of the patients whose wounds disrupted were ambulatory prior to this accident, there is no conclusive evidence that early ambulation increased the incidence of this complication.

The laboratory data associated with 113 cases of wound disruption are given in Table VI. In assessing the protein factor, it should be realized that protein level studies were

done on less than 50 per cent of cases, but of these 19 showed either abnormally low total proteins or a reversed albumin-globulin ratio with lowered serum albumin levels. Of the patients showing hyperglycemia, the majority were under diabetic control, although blood sugar levels were not always maintained within the normal range. Those patients showing lowered hemoglobin levels were frequently in the gynecologic group, where chronic blood loss is a prominent symptom.

Late incisional hernias were known to occur in 11 cases following wound disruption, giving an incidence of 9.7 per cent. This figure is based on cases of those patients who returned to the Royal Victoria Hospital for repair of the hernia, and is probably low as there has been no follow-up in other cases. Mortality following disruption occurred in 17 cases, or 15 per cent, and usually involved poor risk patients who had extensive procedures for malignant disease. In most cases disruption of the operative wound was only one of a number of contributing factors leading to a fatal termination.

DISCUSSION

Despite advances in surgical technique, preoperative and postoperative care, and the control of infection with antibiotics during the last 12 years, the incidence of wound disruption in this hospital has actually increased during this time. In the period from 1941 to 1946, there were 31 disruptions in 10,375 abdominal operations giving an incidence of 0.29 per cent. In the period from 1947 to 1952 there were 82 wound disruptions in 11,936 abdominal operations, an incidence of 0.68 per cent, and this increase runs parallel in the gynecologic and general surgical services. It is difficult to account for this trend, but a widening of indications for surgery to include poorer risk patients and more advanced stages of cancer, with a greater percentage of extensive procedures, plus the fact that more wounds are closed by the resident staff than previously may have some bearing. Certainly the increasing prophylactic use of antibiotics has had no influence on reducing the frequency of this complication, as would be expected if wound infection was an important predisposing factor.

TABLE V.—ASSOCIATED CONDITIONS IN 113 DISRUPTIONS

Associated condition	No. of cases	Per cent
Cough	41	
Vomiting	40	75
Distention	42	
Febrile postoperative	40	35
Gross wound infection	16	13
Drainage through incision	33	30
Previous abdominal surgery	33	30
Malignant disease	24	21

Outstanding in the etiology are mechanical factors leading to increased intra-abdominal tension in the postoperative period. It is thought that the comparatively low incidence of disruption in females is due to a more relaxed abdominal wall following pregnancy and leading to less postoperative tension. This is particularly reflected in the low incidence following cesarean section, when the postoperative abdominal wall is free from excessive strain on the healing wound even in the presence of distention.

It is apparent from these results that the type of suture material used does not, per se, influence the incidence of wound disruption. More important is the careful handling of tissue, in order to eliminate necrotic residue in the wound and to assure close apposition of each layer without undue tension. It is too often not fully appreciated that the tissues and not the suture material are sometimes the weakest link in the chain, and that friable, edematous, or slightly torn peritoneal or fascial layers give way under strain while

TABLE VI.—LABORATORY DATA IN 113 DISRUPTIONS

Laboratory finding	No. of cases	Per cent
Abnormal serum proteins	19	16.8
Hyperglycemia	8	7.1
Hemoglobin		
75+ per cent	77	68.1
60–75 per cent	20	17.7
Less than 60 per cent	10	8.8

the sutures may remain intact. Particular attention should be paid to an exact approximation of the peritoneal layer, as Freeman points out wound breakdown often begins with a tiny wedge of omentum or bowel finding its way through a small peritoneal defect.

Our findings confirm those reported by others that upper abdominal vertical incisions have a higher incidence of disruption than do those in the lower abdomen. We would agree also that midline incisions are more prone to this complication. It is paradoxical to note that operations on the biliary tract, all of which were drained through the incision, showed a lower incidence of disruption than other upper abdominal operations of similar degree. However, this should not absolve drainage through the wound as a predisposing factor of some importance. Drains delay healing, present a weakened area in the course of the wound, and create an avenue of infection. Whenever possible, therefore, drainage should be established through a separate stab wound.

Our findings in respect to protein levels, while limited in number, would tend to show that a lowered serum protein level, particularly the albumin fraction, is an important contributing factor in wound breakdown. This agrees generally with the work of others, and it is our opinion that abnormalities in protein levels would be more frequently found, if sought, and are probably of more significance than hyperglycemic states in this type of case. While patients on the general surgical service did not show a high incidence of anemia, 35 per cent of gynecologic patients with wound disruption showed lowered preoperative hemoglobin levels, all below 75 per cent, and some to a marked degree.

The average age of general surgical patients in this series was 53.3 years, while in the obstetric and gynecologic group it was 45.3 years. While this may reflect in part the age when such groups are most frequently subjected to abdominal operative procedures the fact should be noted that wound disruption in the gynecologic patients is not a complication of the aged, and other factors must be emphasized. The involutional changes occurring at the premenopausal and menopausal age, the frequent symptom of chronic blood loss and resulting anemia and possibly protein deficient states, the frequent use of the lower midline incision, and the tendency in gynecologic surgery to resort to nasogastric suction only after distention is well established are undoubtedly contributory factors.

It has been frequently stated that abdominal operations for malignant disease are more prone to disruption than those performed for nonmalignant conditions. While we have made no observations on the relative incidence in this respect, the comparison of all general surgical disruptions with those occurring in the presence of cancer, on the basis of age, is quite informative. This shows that wound disruptions associated with malignant disease are rare below the age of 50 years and increases steadily with advancing age, accounting for 72 per cent of all disruptions at the age of 65 years and over. It is our impression that this is the result of the process of aging, plus secondary effects of malignant disease, such as debility and anemia rather than a direct effect of the cancer on the healing process. Any elderly patient showing these effects from whatever cause should be considered a potential candidate for this complication.

Many wound disruptions could be prevented by thorough investigation and preoperative preparation of the patient with special reference to acute and chronic respiratory infections and the correction of vitamin and protein deficits and anemia. Following the primary operation, the frequent and early use of nasogastric suction would greatly reduce those mechanical factors which predispose to wound breakdown. The significance of copious serosanguineous discharge as a forerunner should be recognized, and all wounds showing such discharge should be promptly and carefully examined. When disruption is diagnosed, prompt exploration of the wound under proper anesthesia and aseptic conditions should be carried out. Reclosure of the wound with through-and-through sutures of nonabsorbable material has been the method of treatment in the

reat majority of the cases in this series. It s interesting that such resutured wounds arely break down a second time.

SUMMARY AND CONCLUSIONS

1. Factors influencing the process of vound healing have been reviewed.

2. A report is made on 113 cases of wound lisruption, occurring in 22,311 major abdominal operations performed in the Royal 'ictoria Hospital in the 12 year period from 941 to 1952.

3. The overall incidence was 0.51 per cent.)n the general surgical service the incidence as 0.47 per cent in 15,711 operations, while n the obstetric and gynecologic services the ncidence was 0.59 per cent in 6,600 procedures.

4. Upper abdominal incisions were more rone to this complication (0.94 per cent incidence) than were those in the lower abomen (0.54 per cent). No McBurney incisions disrupted and hence they were excluded from the above.

5. The type of suture material did not appear to have any effect on the incidence of vound disruption. The value of tension sutures as a prophylactic measure in closure vas not established by our findings.

6. Mechanical factors leading to increased ension in the healing abdominal wall were present to an excessive degree in 75 per cent of disruptions. These factors, usually caused by cough, vomiting, or distention in the postoperative phase, are, therefore, considered to be of great importance in the etiology of this complication.

7. The factors of advanced age, poor nutrition with or without detectable serum protein deficiencies, anemia, and drainage through the incision are thought to be significant. Wound infection is considered to play only a minor role, as the widespread use of antibiotics has not decreased the incidence.

8. Late incisional hernia occurred following wound disruption in at least 9.7 per cent of cases, and the mortality was 15 per cent in this series.

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THE EFFECTS OF INTRAVENOUS FLUIDS ON CEREBROSPINAL FLUID PRESSURE

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IN their pioneering experiments Weed and McKibben demonstrated that a change in the osmotic concentration of blood plasma is followed by a reciprocal change in the hydrostatic pressure of the cerebrospinal fluid. Since then, therapy based on this reaction has been clinically used in neurosurgery, especially in cases of increased intracranial pressure. A large number of papers dealing with the acute effect of intravenous infusion of hypertonic solutions in reducing cerebral hypertension have been published.

Less attention has been focused on the question, what is the effect on cerebrospinal fluid pressure of the solutions commonly used to maintain water balance of patients unable to take fluids by mouth? The importance of answers to this question are manifest when one considers that the majority of neurosurgical patients will require intravenous fluid therapy during operation and a significant number will need parenteral fluids for several days afterward. The margin of safety between tolerated and fatal increases in intracranial pressure in such patients is frequently small. Furthermore, there is a significant mortality among successfully operated upon brain tumor patients due to late increases in cerebrospinal fluid pressure which cannot be alleviated with hypertonic solutions or repeated ventricular tappings.

In clinical practice, blood transfusions given during the operative period are most commonly followed by infusions of 5 per cent glucose in distilled water. This solution is isotonic and has been considered preferable to saline since edema is so frequently associated with sodium administration. The papers of Coller and Maddock (2, 3) have emphasized the impaired ability of the kidneys to eliminate salt in the early postoperative period and the resultant tendency of the body to retain water if sodium chloride is added. On the other hand, little attention has been directed to the possibility that isotonic glucose infusions may act to elevate cerebrospinal fluid pressure. Such a reaction would not be surprising when one considers the fact that the glucose entering the body is rapidly metabolized or converted to glycogen. A large volume of water thus metabolically divested of the solute to which it owed its original isotonicity may then act to dilute blood plasma and interstitial fluid. An osmotic gradient is produced, which favors the transfer of water to the cerebrospinal fluid causing a marked increase in intracranial pressure.

The studies to be reported concern an investigation of the effects on cerebrospinal fluid pressure of intravenous infusion of a number of commonly used solutions, including 5 per cent glucose.

MATERIALS AND METHODS

The subjects of these experiments were patients with malignant brain tumors except in 3 instances in which the diagnoses were, respectively, chronic subdural hematoma, epidural bleeding, and ruptured aneurysm with subarachnoid hemorrhage. In the tumor cases, internal decompression and in some cases lobectomy had been performed several weeks prior to study, except in 1 patient in whom observations were made 4 days postoperatively. The clot of the patient with chronic subdural hematoma had been evacuated 2 months prior to study, but there had been failure of the brain to re-expand.

All of the patients were comatose or semicomatose. They had been on daily tube feed-

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TABLE I.—SUMMARY OF RESULTS

Infusion			Patient			Spinal fluid		
Solution	Amount, c.c.	Rate, c.c./min.	Name	Age, years	Disease	Initial pressure, mm.	Maximal response, mm.	Per cent
5% glucose in distilled water	1500	11	J. W. ♂	52	Subarachnoid hemorrhage	230	280	+ 22
	1500	6	J. W. ♂	52	Subarachnoid hemorrhage	330	480	+ 45
	1200	6	V. J. ♂	28	Glioblastoma	200	270	+ 35
	1500	15	H. A. ♂	59	Metast. ca of brain	150	300	+100
	1000	11	H. A. ♂	59	Metast. ca of brain	280	400	+ 43
	1000	11	P. N. ♂	74	Subdural hematoma	150	300	+100
	1000	7	M. O'N. ♀	53	Glioblastoma	700	800	+ 14*
5% glucose in 0.85% NaCl	1500	8	J. W. ♂	52	Subarachnoid hemorrhage	280	140	− 50
	1200	9	D. S. ♂	60	Epidural hemorrhage	230	170	− 26
	1000	11	H. A. ♂	59	Metast. ca of brain	300	200	− 33
	1000	11	P. N. ♂	74	Subdural hematoma	150	100	− 33
2.5% glucose in 0.42% NaCl	1200	6	V. J. ♂	28	Glioblastoma	130	120	− 8

*Patient was in a terminal state.

ings for days or weeks prior to study and were in a reasonably good state of hydration and electrolyte balance. All showed stable, though not necessarily normal, cerebrospinal fluid pressures.

The solutions studied were 5 per cent glucose in water, 5 per cent glucose in 0.85 per cent saline, and 2.5 per cent glucose in 0.42 per cent saline. The rate of infusion was kept constant in individual experiments, but was varied in different observations from 6 to 15 milliliters per minute. The total amount of fluid infused varied from 1,000 to 1,500 milliliters.

The patients lay on their sides or back, maintaining the same position throughout the 3 to 5 hour period of study. Cerebrospinal fluid pressure was measured without losses by means of a lumbar needle or intraspinal catheter attached to a Sanborn electromanometer. Measurements were begun about 1 hour before the start of the infusion to ascertain a reasonable baseline. In 5 cases, several days following the initial experiment, the infusion was repeated under identical conditions except that plasma and spinal fluid samples (not exceeding 2.0 ml. in volume) were collected at the following intervals: at the start of infusion, at the height of the spinal fluid pressure response or when 50 per cent of the infusion was completed, or both, and again at the end of the infusion. These samples were analyzed for total osmotically effective solute concentration using a modified Fiske, model B osmometer.

RESULTS

In Table I the effects of the various solutions on the cerebrospinal fluid pressure of the patients studied are summarized. It will be noted that 5 per cent glucose in distilled water resulted in a significant increase of the spinal fluid pressure in every patient. The increase is roughly correlated with the rate of infusion, the increase in pressure being generally greater if the rate was above 10 milliliters per minute. Increases in pressure were not correlated with the infusion volume in the present studies. The largest pressure increments were generally observed in patients in whom the initial cere-

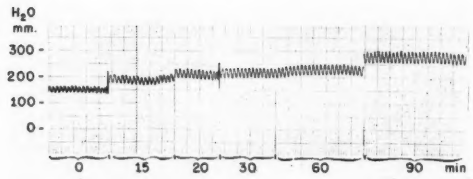

Fig. 1. Patient H.A. Spinal fluid pressure at different time intervals following the start of an intravenous infusion of 1,500 cubic centimeters of 5 per cent glucose in water at a rate of 15 cubic centimeters per minute.

brospinal fluid pressure was normal or only slightly elevated (Fig. 1).

Infusion of 5 per cent glucose in 0.85 per cent saline regularly acted to reduce cerebrospinal fluid pressure (Fig. 2). In the 4 studies using this solution the decrement ranged from 50 to 74 per cent of the starting pressure.

The infusion of 2.5 per cent glucose in 0.42 per cent saline was studied on only 1 occasion. The data indicate that the infusate was essentially without influence on this patient's cerebrospinal fluid pressure.

The measurements of total osmotically effective solute concentration in serum and spinal fluid samples during infusions of these solutions indicate that the acute changes in hydrostatic pressure of the spinal fluid are correlated with the expected transfer of water, in accordance with the direction of the osmotic gradient (Fig. 3). The serum solute concentration fell rapidly during the infusion of 5 per cent glucose in water. A similar, but later change was observed in the spinal fluid. During the period when the serum was hypotonic relative to the spinal fluid, cerebral hypertension was observed. However, little change in serum concentration was seen with the infusion of 2.5 per cent glucose in 0.42 per cent saline. The

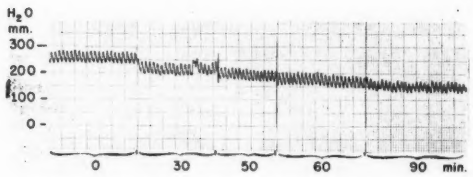

Fig. 2. Patient J.W. Spinal fluid pressures following the start of infusion of 1,500 cubic centimeters of 5 per cent glucose in physiologic saline at the rate of 8 cubic centimeters per minute.

small changes observed in serum were paralleled by similar changes in spinal fluid so that the osmotic relations between the two compartments were essentially undisturbed. Measurements made during the infusion of 0.85 per cent sodium chloride indicate that the fall in spinal fluid pressure was coincident with a decrease in the osmotic gradient between serum and spinal fluid.

DISCUSSION

Theoretical considerations of changes in intracranial pressure are hampered by our incomplete knowledge of the factors concerned in the regulation of cerebrospinal fluid pressure. Some of the important hydrodynamic factors include the balance between the production and absorption of the cerebrospinal fluid (including the largely theoretical "secretion pressure"), the elasticity of the meninges, the hydrostatic pressure, the capillary pressure of the choroid plexus and/or the meninges, and the closely related, but by no means identical, intracranial venous pressure. In addition, the osmotic balance between the plasma and the cerebrospinal fluid appears to exert an important influence on cerebrospinal fluid pressure. When there is no change in the other major factors, change in the osmotic gradient becomes the chief determinant of changes in spinal fluid pressure. This is evident from the experimental demonstrations of the effect on spinal fluid pressure of injections of hypertonic and hypotonic solutions.

Hydrodynamic factors, important as they are, show little variation within the same patient whose vital signs are steady and stable, whose clinical course is unchanged, and in whom the pressure measurements are performed in the same position and under identical technical conditions. The only significant variable factor in the patients, considered in the present study, was the osmotic pressure of the plasma and the differential in osmotic pressure relations between the plasma and cerebrospinal fluid. Changes in the latter were almost immediately followed by changes in spinal fluid hydrostatic pressure.

In clinical practice a 5 per cent glucose solution in water has long been considered to be a safe solution for use in neurosurgical

patients. Some data have already been published pointing out the danger of using this solution in large amounts and indiscriminantly in patients with increased intracranial pressure. However, these recommendations have not been given adequate consideration since the results were obtained in animal experiments and the final conclusions were thought to be not readily applicable to humans. In the light of the findings in the present study, a brief review of the earlier data may be of interest.

Webster and Freeman studied the cerebrospinal fluid pressure in normal dogs and in animals with severe head injuries. They noticed that intravenous administration of a 5 per cent glucose solution in water produced a moderate increase in the spinal fluid pressure. Wilson, Jones, Coleman, and Moyer discovered that in dogs, 7 milliliters of 5 per cent glucose in water per kilogram of bodyweight, when administered intravenously, approximately doubled the cisternal pressure. They were led to suggest that 5 and 10 per cent solutions of glucose in water should not be given during the course of intracranial operations. More recently, Fishman (4) described the effects of various intravenous solutions on a normal and increased intracranial pressure of dogs. He injected solutions of 5 per cent glucose in water, 5 per cent glucose in isotonic saline, and isotonic saline alone and recorded the cerebrospinal fluid pressure in the cisterna magna. Large volumes (5 to 50 c.c. per kilogram of body weight) were injected very rapidly over a 5 minute period in order to increase the magnitude of response. For this reason, the effect of the intravenous solutions was of comparative value only. The increase in cerebrospinal fluid pressure following administration of 5 per cent glucose in water was about twice that following administration of an equal volume of isotonic saline. The pressure response following the administration of 5 per cent glucose in saline was essentially the same as the response to isotonic saline alone. Fishman likewise concluded on the basis of these experiments that the administration of 5 per cent glucose in water to patients with increased intracranial pressure is likely to be hazardous. He was cautious, however, in applying these data to clinical situations. In 2 human subjects with normal intracranial pressures, several months after severe head injury, infusion of 1,500 cubic centimeters of either 5 per cent glucose in water or isotonic saline over a 60 to 90 minute period did not affect the cerebrospinal fluid pressure (5).

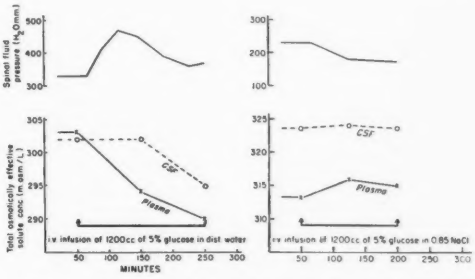

Fig. 3. Changes in the total osmotically effective solute concentrations of plasma and cerebrospinal fluid and their effect on spinal fluid pressures during the infusion respectively of 5 per cent glucose in water and 5 per cent glucose in physiologic saline.

The data of the present investigation indicate that at rates of delivery commonly used in clinical practice, intravenous infusion of a 5 per cent glucose solution in water is followed by a significant increase in spinal fluid pressure. In some patients, this increase may reach a dangerous level. The pressure rise is correlated with a reduction of the total osmotically effective solute concentration of the plasma. This latter change is primarily due to the rapid metabolism of the glucose originally contained in the fluid infused. The extent of reduction in plasma solute concentration is dependent upon such factors as the rate of delivery of the fluid and the rate of glucose metabolism. It may be particularly large for this type of infusion fluid as compared to some others because the body is not as readily able to eliminate the excess water. As Talbot, Crawford, and Butler pointed out, water retention occurs with smaller volumes of infusates if they contain only glucose than with infusates which also contain 75 mosM. or more per liter of electrolyte solute. In addition, it is probable that the relatively easy access of glucose into the cerebrospinal fluid plays a part in the cerebral hypertension re-

sulting from the use of the former type of solution. In the early phase of administration, when blood sugar concentration is elevated, glucose concentration in the cerebrospinal fluid also tends to rise. Later, though during continued infusion, the rapidly increasing glycogenic response lowers blood sugar concentration so that it may fall below that of the cerebrospinal fluid. This favors the transfer of water from plasma to the cerebrospinal fluid and is, indeed, the reaction which has led to the virtual abandonment of 50 per cent glucose infusion in the emergency treatment of patients with elevated spinal fluid pressure (1).

Infusions of 5 per cent glucose in 0.85 per cent saline at similar rates of delivery were accompanied in the subjects of this study by diminution of cerebrospinal fluid pressure. While in certain neurosurgical patients this may be a desirable trend, the sodium content of quantities of such an infusate adequate to maintain water balance are not readily excreted by the ill patient and edema formation is apt to result. The infusion of 2.5 per cent glucose in 0.45 per cent sodium chloride was observed to cause little disturbance in cerebrospinal fluid pressure or the osmotic relations between the plasma and spinal fluid in patients studied in this investigation. As Talbot has pointed out, much smaller total quantities of such a solution are required to maintain water balance in the seriously ill patient and these quantities deliver amounts of sodium which are more readily excreted if need be. He has advocated this type of infusate for use in severely sick patient with a variety of different types of illness. The present investigation indicates that the same type of fluid replacement can also be considered safe for use in patients with increased intracranial pressure.

SUMMARY

The effect of various intravenous solutions on cerebrospinal fluid pressure and on the osmotic concentration of plasma and cerebrospinal fluid was studied in humans with normal as well as with increased intracranial pressure.

Intravenous infusion of 5 per cent glucose in water produced an osmotic gradient favoring the transfer of water to the cerebrospinal fluid and was followed by a significant increase in the intracranial pressure. Five per cent glucose in physiologic saline acts in the opposite way and reduces the spinal fluid pressure.

The use of a 2.5 per cent glucose in 0.42 per cent sodium chloride solution has been found to cause little disturbance in cerebrospinal fluid pressure. For this reason and because administration of larger proportions of sodium chloride to sick postoperative patients would lead to salt retention and the formation of edema, this electrolytically hypotonic glucose solution is advocated in maintaining the fluid balance in patients with increased intracranial pressure.

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HISTOPLASMOSIS: CLINICAL AND PATHOLOGIC STUDY OF 20 CASES

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THE purpose of this paper is to present a review of the clinical and pathologic characteristics of histoplasmosis as observed in all cases of this disease encountered at the Mayo Clinic. A review of the literature will not be presented, as this has been done adequately by numerous authors such as Meleney and Hodgson and co-workers.

In a review of our files, we found records of 20 cases in which a diagnosis of histoplasmosis was made. The diagnosis was proved by culture in all but 1 of the cases (Case 12, Table I). This case was accepted in our series because the pathologic and clinical picture was consistent with that of histoplasmosis, and the organisms seen on microscopic section were typical of Histoplasma capsulatum. We sent letters to the 6 patients who had not been seen at the clinic within the past 6 months, and the replies indicated that 1 patient had died and 4 others were living and well; we did not hear from 1 patient (Case 10, Table I).

In the following pages we present (1) a review of the pathologic characteristics of histoplasmosis, (2) the significant clinical and laboratory findings in the 20 cases of our series, and (3) detailed reports of certain more or less typical cases.

PATHOLOGIC CHARACTERISTICS

Histoplasmosis is a granulomatous disease caused by the fungus, Histoplasma capsulatum. Conant, in 1941, made cultural studies of this organism and was able to complete the life cycle by use of blood agar slants sealed with paraffin. He placed the fungus in the group, Moniliaceae, of the Fungi imperfecti. DeMonbreun could complete the life cycle only by passing the mycelial form through animals.

The pathologic characteristics of this disease are illustrated in Figures 1 to 4. The granuloma which this fungus produces is a small collection of epithelioid cells, intermixed with foreign body giant cells and surrounded by small mononuclear cells resembling lymphocytes. Figure 1b illustrates the typical granulomatous lesion very well. Occasionally in the center of the granuloma there is necrosis. The lesion greatly resembles that produced by tuberculosis, coccidioidomycosis, brucellosis, sporotrichosis, kala-azar, and sarcoidosis, and there is nothing pathognomonic on microscopic section to differentiate them unless organisms are visible. Bacteriologic isolation of the organisms is the only means of proving definitely that an infection is present. Although merely observing the organisms on section or smear frequently permits the making of a tentative diagnosis, nevertheless a culture should be made to differentiate the condition with certainty from leishmaniasis, toxoplasmosis, cryptococcosis, or the so-called microforms of blastomycosis.

In all our cases in which sections were available, examination revealed either caseating or noncaseating tubercles, the latter type predominating. In 12 cases Histoplasma capsulatum was seen in one or more sections or smears when we were cognizant of the presence of this disease. The organisms were most frequently intracellular, although occasionally they were seen extracellularly.

The giant cells may be filled with organisms. The presence of these organisms may be

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TABLE I.—CLINICAL DATA IN 20 CASES OF HISTOPLASMOSIS

	Case No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Age, years	34	60	27	54	34	23	36	30	34	36	47	47	70	7 mo.	48	32	35	44	74	42	To-tal
Anemia								3-4			3-4			3.6							3
Anorexia	+			N						N				N		N	+	+	+	+	5
Blastomycin test					N		N			N								N		N	0
Cancer of lung		+																			1
Chest pain	+	+	+	+				+		+						+		+		+	9
Chills					+		+	+			+					+		+			6
Coccidioidin test		N	N				N		N	N							N	N		N	0
Cryptococcosis								+													1
Cough		+	+	+	+		+		+	+	+		+			+	+	+		+	13
Culture	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	19
Diabetes											+										1
Diarrhea								+							+					+	3
Death					+	+	+	+			+	+	+	+	+	+	+				11
Dyspnea		+									+					+	+	+			5
Effusion		+		+												+		+			4
Endocarditis												+									1
Fatigue		+			+	+	+	+	+	+	+	+		+	+	+	+	+		+	15
Fever	+	+			+	+	+	+	+	+	+	+	N	+	+	+	+	+		+	16
Flocculation (syphilis)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0
Hemoptysis																+				+	2
Hepatomegaly		+									+	+	+	+	+	+	+		+		9
Complement fixation (histoplasma)								+													1
Histoplasmin test		+	+	+	N		N		+	N	N		N	N			N	N		N	4
Hodgkin's disease	+																				1

N = Negative
+ = Positive

brought out more clearly by special stains such as the Giemsa or Best-Bodian stain.

The original description of the fungus by Darling has not been improved upon, and is, therefore, quoted here: "The organism is primarily intracellular and is oviform or round surrounded by a clear, refractile achromatic zone or capsule, giving the impression of an encysted protozoan. The structure is not stained homogeneously, but very irregularly, rarely any two looking exactly alike. The body consists of a deeply staining light blue with a polychrome stain, with achromatic spaces resembling vacuoles. The deeply staining substance, or chromatin, is practically always heaped up along one end of the body, sometimes consisting of a single mass or several small masses of chromatin. Sometimes it is ring shaped and occasionally extended along half of the periphery of the body, being crescent in shape. Occasionally a chromatin dot or rod is seen near the larger chromatin body. This dot or rod is sometimes at the opposite end or side of the body. The faintly staining blue substance takes up the rest of the space except where there is one or more small achromatic zones, resembling vacuoles of protozoan. These vacuoles are irregularly placed being sometimes near the periphery of the body."

This disease may cause large abscesses such as those we have seen in the adrenals and lungs, or only small miliary nodules (Figs. 1a and 2, inset).

TABLE I.—CLINICAL DATA IN 20 CASES OF HISTOPLASMOSIS—Continued

	Case No.																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Age, years	34	60	27	54	34	23	36	30	34	36	47	47	70	7 mo.	48	32	35	44	74	42	To-tal
Hypersplenism											+										1
Jaundice														+		+					2
Joint pain						+		+			+										3
Lymphadenopathy	+				+	+		+			+				+	+			+		8
Melena									+						+	+					3
Muscle pain	+				+				+		+		+								5
Nausea, vomiting											+				+		+				3
Operation			+						+	+										+	4
Petechiae												+									1
Positive chest x-ray	+	+	+	+	+	+	+	+	+	+	N	N	N			+	+	+		+	14
Sedimentation rate	31	81	8		39		6	113	55	45								104	30	16	
Sex	M	F	F	M	M	M	M	M	F	M	M	M	M	F	M	M	M	F	M	M	
Skin pigment								+			+										2
Smears	N	N	+	N	+	+	+	N	N	+	N	+	+	+	+	+	N	N	N	N	10
Sore throat					+	+	+		+			+	+	+	+	+		+	+		11
Splenomegaly											+	+	+	+	+	+	+				7
Sweats		+				+				+	+					+		+			6
Tinnitus						+															1
Tuberculin test		+	+		N	N	N		N	+	+	N		N				N		N	4
Tuberculosis																		+			1
Urinary albumin						+		+				+			+	+	+		+		7
Weight loss		+		+	+	+	+	+		+	+	+	+	+	+	+		+	+	+	16

N—Negative
+—Positive

OBSERVATIONS IN 20 CASES

The clinical findings present in our 20 cases at one time or another are given in Table I. It is of interest that in 11 of the 20 cases the patient had a severe sore throat or mouth on some occasion, and in several this was the presenting and primary symptom. To be noted also was the frequent occurrence of chest pain, productive cough, loss of weight, fatigue, and fever, chills, and sweats. The positive roentgenographic findings in the chest during illness consisted of nodules, cavities, infiltrations, effusions, and fibrosis. The hepatomegaly present in 9 cases was not noted in 2 cases prior to necropsy, while the splenomegaly present in 7 cases was not noted in 3 cases prior to necropsy.

The results of skin tests with tuberculin, blastomycin, and coccidioidin were not remarkable. On the other hand, the reaction to the histoplasmin skin test was positive in 4 of the 13 cases in which it was performed. The positive reactions were graded 2, 3, 2, and 2 respectively (on a basis of 1 to 4).

The anemia referred to in 3 cases was represented by erythrocyte counts of 3,400,000, 3,400,000, and 3,600,000, respectively, per cubic millimeter of blood. Also present were leucocytosis in 2 cases, leucopenia in 5 cases, and lymphocytosis in 3 cases. The sedimentation rate was elevated in 8 of the 11 cases in which it was determined. The lymphadenopathy present in 8 cases was either local or generalized.

In all cases but 2 (Cases 12 and 17) the diagnosis of histoplasmosis was made during life. In this connection it is pointed out that Histoplasma capsulatum was recovered in all

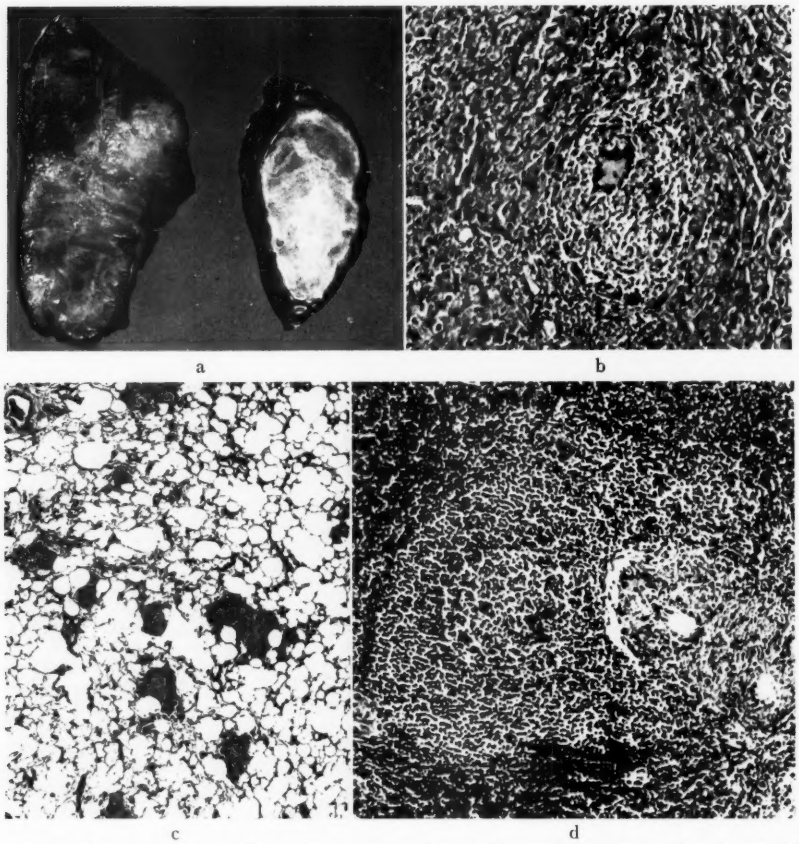

Fig. 1. Case 11. a, Adrenal gland. The gross architecture is completely destroyed and replaced by caseous material. Microscopically, no normal architecture was seen. This demonstrates how completely the adrenal gland may be destroyed, so that symptoms of adrenal insufficiency may ensue. b, Liver. The granulomatous lesion, with a single giant cell in the periphery, is similar to those seen in any granulomatous disease. Hematoxylin and eosin, ×95. c, Lung. Numerous tubercles are present. Hematoxylin and eosin, ×11. d, Spleen. Numerous tubercles similar to this were distributed uniformly throughout the organ. Hematoxylin and eosin, ×95.

the 19 cases in which cultures were made, and that organisms thought to represent Histoplasma capsulatum were observed in smears or microscopic sections of tissue from 12 of the 20 cases. There seems to be no significance in the fact that in 1 case each Hodgkin's disease, hypersplenism, diabetes mellitus, tuberculosis, or cryptococcosis was an associated condition. Two patients had clinical evidence suggestive of Addison's disease.

Data as to the organs affected in our series of cases are of interest. These data are based on necropsy or very suggestive clinical evidence. In 14 cases there was pulmonary involvement; in an additional case there were highly suggestive clinical reasons for believing that such involvement was present. In 3 cases there was no evidence of pulmonary involvement, but in 1 of these the mediastinal nodes were affected by Hodgkin's disease, histoplasmosis, or both. The oropharynx, liver, and spleen were the next most common structures to be affected, each being involved in 7 cases. In an additional case the oropharynx

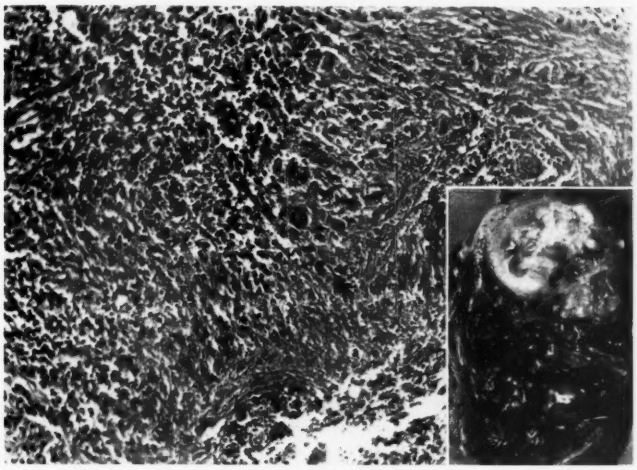

Fig. 2. Case 3. Section of the surgical specimen from the lung. Several giant cells are visible, and there is a marked fibrotic reaction surrounding the lesion. No organisms were seen in the histologic sections. The lesion is similar to that of tuberculosis. Hematoxylin and eosin, ×125. Inset, Portion of the surgical specimen demonstrating the evacuating lesion which may be found in involvement of the lung with histoplasmosis. There is nothing grossly specific in such a lesion to differentiate it from any other excavating lesion.

was thought to be affected but this could not be proved. The adrenals were involved in 6 cases, and in the seventh there was clinical evidence of the disease in these organs. The peripheral lymph nodes were affected in 7 cases. The bone marrow was proved to be involved in 5 cases, and in 3 cases it was the first tissue to yield positive evidence of histoplasmosis.

We found that the incidence of the disease in the lungs was much greater in our series of cases than in the series reviewed from the literature, while the sex distribution of the patients was about the same. The ages ranged from 7 months to 74 years. Most of our patients came from the central states around the Mississippi River. The fact that in all but 2 of the cases (Cases 12 and 17) the diagnosis was made before death, which represents a much better result than that which is reported in the literature, probably can be attributed to a number of factors, among which is the fact that bacteriologist, surgeon, and pathologist have been impressed with the necessity of co-operating in attempting to diagnose infections.

The results of the various skin tests in our series are consistent with those reported in the literature in the respect that they are not reliable as an exclusion test.

Since Darling first described histoplasmosis it was considered a universally fatal disease up until 1943 when Long and Sterns suggested that a mild form exists. In our series of cases 11 deaths had occurred at the last report. One of our living patients also had Hodgkin's disease while another also had carcinoma of the lung (Cases 1 and 2) respectively; hence, in these cases the prognosis is grave irrespective of the histoplasmosis. One patient (Case 4) wrote us that he is back to full time work, his only complaint being that he tires easily; he received no specific treatment during his illness. Four patients (Cases 3, 9, 10, and 20) underwent resection for their pulmonary lesions and were doing well when last heard from. It appears that in 2 of our cases the lesions probably healed spontaneously while in 3 cases they may have been cured by surgical treatment. One patient (Case 19) should have a poor prognosis if our other cases of oropharyngeal involvement are any indica-

Fig. 3. Labial lesion in a case of histoplasmosis. There is nothing specific about the gross appearance of this lesion that would aid in differential diagnosis. Histoplasma capsulatum was cultured from scrapings from the lesion.

tion. Another patient (Case 20) may do poorly because extensive involvement of one lung was found and involvement of the other was suspected. Although the prognosis in clinical histoplasmosis is poor, there is still some hope. For those patients with operable pulmonary lesions the prognosis may even be good.

The coexistence of histoplasmosis with other diseases has been mentioned in the literature on numerous occasions. As previously mentioned, we had several cases in which other diseases coexisted. In Case 11 the condition was clinically indistinguishable from hemolytic anemia, and only after bone marrow biopsy had disclosed granulomas was it suspected that the patient might have a granulomatous infection. It was still believed that splenectomy would improve the blood picture, which it did. Culture of the spleen gave positive evidence of histoplasmosis. The question arises: Did infection of the spleen with Histoplasma capsulatum cause this organ to have an inhibiting effect on the formation of erythrocytes or a destructive effect on the erythrocytes themselves, or was the condition with respect to the erythrocytes only a coincidental finding? This patient's diabetes mellitus, because it may have lowered his resistance to infection, possibly was a predisposing factor in his contraction of histoplasmosis. The diabetes might even have been caused by infection of the pancreas with Histoplasma capsulatum in a mild form several years previously, and the last illness could have represented merely a reactivation of the histoplasmosis.

In Case 2 the patient had a coexisting pulmonary carcinoma on the left side. It was considered by the consulting surgeon to be inoperable because of a lesion in the right side that resembled a metastatic growth and because of pleural effusion with positive cytologic evidence of malignancy. The question arises here whether a left pneumonectomy would have helped this patient, as the lesion on the right side might have been due to histoplasmosis. This patient might have had dormant histoplasmosis which was activated by the carcinoma.

In Case 18 the patient had been treated several years for tuberculosis, said to have been proved at a sanatorium. Histoplasma capsulatum was cultured from the pleural fluid. Possibly this patient had histoplasmosis originally, or the histoplasmosis could have been inactive or quiescent only to be reactivated by the tuberculosis, or Histoplasma capsulatum could have been introduced on one of the occasions when pneumothorax occurred.

The finding of Cryptococcus neoformans on culture in Case 8 was evidence that cryptococcosis and histoplasmosis coexisted.

It was interesting to see that the adrenal glands were involved in 6 of our cases. In 2 of these cases there was clinical evidence suggestive of Addison's disease. As has been pointed out by Hodgson and co-workers, histoplasmosis must be considered as an etiologic agent in Addison's disease. Our small series certainly substantiates this point. Formerly, tuberculosis was thought to be probably the commonest etiologic agent in Addison's disease. It is likely, however, that in some of the cases the disease was actually caused by Histoplasma capsulatum but that the similarity in pathologic pictures resulted in the erroneous diagnosis of tuberculosis.

For patients with oropharyngeal lesions or with albumin and casts in the urine, the prognosis is grave. In our series of 11 deaths, all but 1 patient had either an oral lesion or renal involvement.

The tissues and the methods used in making the initial diagnosis of histoplasmosis in our series are indicated in Table II. It is evident that a variety of tissues yielded positive or presumptive evidence of the disease. In 3 cases the initial diagnosis was made from pleural fluid. In 4 cases biopsy culture or smears from the mouth or throat disclosed the

nature of the disease. The sputum was positive for Histoplasma capsulatum in 4 cases and the bone marrow was positive in 3 cases. The liver, a supraclavicular node and a gastric washing presented positive evidence in 1 case each, and the lung presented positive evidence in 2 cases. In 4 of the cases granulomatous areas were seen only on section but these were enough to make us continue our efforts to isolate the organisms. It is important to mention here that in taking tissue for section and culture one must be sure that an adequate amount is obtained, for often the organisms are so sparsely distributed that they will not be found in cultures or sections. If large enough specimens are obtained, cultures for tubercle bacilli, ordinary bacteria, and various fungi may also be made.

REPORT OF ILLUSTRATIVE CASES

CASE 3. A 27 year old white housewife from Minnesota was first seen at the Mayo Clinic in March, 1951. Her grandmother and 1 paternal aunt had died of tuberculosis, but the patient had had no contact with either. Her present illness had begun in March, 1950, when a roentgenogram showed a "lesion" in the left lung. She had no symptoms at that time. In May, 1950, a "cold" with cough and the production of a minimal amount of sputum developed, but this condition subsided promptly. She noted some pain in the anterior part of the left side of the chest at the time. Still symptom free, she had another roentgenogram of her chest and entered a sanatorium for diagnosis and treatment. There she was placed at rest in bed. Three gastric washings and 3 specimens of sputum were negative by smear and culture for tubercle bacilli. The tuberculin skin reaction also was negative. In January, 1951, she was started on treatment with streptomycin and PAS (para-aminosalicylic acid) given 3 times a week. After 1 month, streptomycin was given only 2 times a week and PAS was given every day for 3 months. She felt well throughout her course of treatment. She was referred to the Mayo Clinic from the sanatorium, with an indeterminate lesion of the left lung.

Physical examination at the clinic revealed a small sinus that opened along the sternocleidomastoid muscle on the right side. The results of laboratory examination were as follows: urinalysis, negative; hemoglobin, 12.5 grams per 100 cubic centimeters of blood; leucocytes, 4,400 per cubic millimeter of blood; lymphocytes, 20 per cent; monocytes, 1 per cent; polymorphonuclear leucocytes, 77.5 per cent; eosinophils, 0.5 per cent; and sedimentation rate, 8 millimeters in 1 hour (Westergren method). A roentgenogram at that time disclosed what was thought to be a cavitating lesion in the left upper lobe in the first anterior interspace. The coccidioidin skin test as well as the tuberculin skin test with first strength purified protein derivative (PPD) gave negative results. The tuberculin test with second strength PPD gave a grade 2 reaction (on a basis of 1 to 4). The patient was advised to have an exploratory thoracotomy to determine the nature of the lesion.

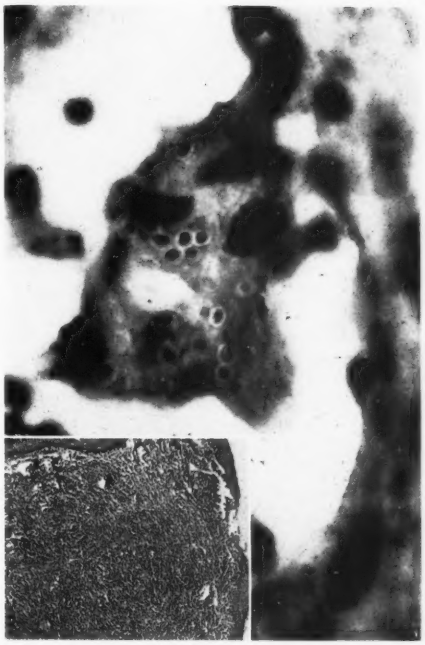

Fig. 4. Case 13. Biopsy specimen from an ulcer in the pharynx. Histoplasma capsulatum organisms are visible within a multinucleated giant cell. Hematoxylin and eosin, ×1,200. Inset, There is marked chronic inflammatory reaction but no tubercles are visible. Hematoxylin and eosin, ×27.

In May, 1951, a segmental resection was performed on the left upper lobe. The pathologic examination of the specimen disclosed a granuloma 2.5 centimeters in diameter that contained a cavity 2 centimeters in diameter. Culture of this specimen for tubercle bacilli and Brucella abortus gave negative results. Examination of a smear as well as 2 guinea-pig inoculations for tubercle bacilli gave negative results. Culture for fungi revealed Histoplasma capsulatum. Review of the sections of tissue disclosed masses of Histoplasma capsulatum organisms in necrotic material. The histoplasmin skin test performed postoperatively gave a grade 3 reaction (on a basis of 1 to 4).

The patient made an uneventful postoperative recovery and no further treatment was required.

TABLE II.—TISSUES AND METHODS USED IN MAKING THE INITIAL DIAGNOSIS OF HISTOPLASMOSIS

Case No.	Tissue	Method
1	Supraclavicular node	Culture
2	Pleural fluid	Culture
3	Lung (segmental resection)	Culture
4	Pleural fluid	Culture
5	Bone marrow	Culture
6	Oropharynx	Direct smear
7	Sputum	Direct smear
8	Gastric washings	Culture
9	Sputum	Culture
10	Sputum	Culture
11	Spleen	Culture
12	Liver (biopsy)	Tissue section
13	Oropharynx	Direct smear
14	Bone marrow	Culture
15	Larynx	Biopsy section
16	Bone marrow	Direct smear
17	Lung (post mortem)	Culture
18	Pleural fluid	Culture
19	Lesions of gum	Culture
20	Sputum	Culture

When last heard from in October, 1952, she was completely symptom free and doing well.

CASE 4. A 54 year old white carpenter, first seen at the Mayo Clinic in March, 1951, had experienced, in 1947, the sudden onset of pain in the right lower part of the chest. The pain was made worse by deep breathing and by lying on his right side, but it was relieved somewhat by a tight belt applied to the chest. This pain continued up to the time of admission but had become much less severe. Beginning February 16, 1951, he had received a daily injection of penicillin for 8 days after a roentgenogram had disclosed an egg-shaped mass at the cardiophrenic angle in the left side of the chest. After this treatment the mass had not changed. Beginning on February 24, 1951, he had noticed for a few days a slight burning sensation in the anterior portion of the right side of the chest on breathing. On March 1, 1951, a slight cough productive of 3 tablespoonfulls of white sputum a day had developed. He had not noticed any hemoptysis, dyspnea, or dysphagia, and his appetite had not changed. He had lost approximately 10 pounds (4.5 kgm.).

When the patient was admitted to the clinic his blood pressure was 130 millimeters of mercury systolic and 70 diastolic, and he was obese. The results of laboratory examination on March 9, 1951, were as follows: hemoglobin, 12.7 grams; erythrocytes, 4,480,000; leucocytes, 6,400; eosinophils, 2.5 per cent; and urinalysis, negative. A roentgenogram of his chest revealed a large right hilus, fibrosis in the right lower lobe, and pleural thickening or effusion at the right base. There seemed to be some loss of the volume of the right lower lobe which may have been due to obstructive pneumonitis. The results of sputum examination for malignant cells were negative on 3 occasions. Thoracentesis gave a blood tinged fluid which did not contain malignant cells but which was found, on culture, to contain Histoplasma capsulatum. Smear and culture of the pleural fluid did not disclose tubercle bacilli. Bronchoscopy gave negative results. No specific treatment was given.

The patient was dismissed but seen monthly up to August, 1951. He seemed to be improving during this period. In August a roentgenogram of his chest showed considerable improvement over the original. He was resting a great deal and was returning to work gradually.

In October, 1952, he wrote that he was feeling well and that he was back at work full time. His only complaint was that he tired easily.

CASE 16. A 32 year old white salesman from Indiana, who was first seen at the Mayo Clinic in September, 1950, had been rejected from the Army because of hypertension. His present illness began about 4 years prior to admission when a sore throat developed. His local physician made a diagnosis of streptococcic sore throat. He was treated with sulfonamide drugs and penicillin, but his condition became much worse and ulcers developed on his palate and tongue. He had no fever at that time and he felt well except for the sore throat. For the next 3½ years he had continued to have trouble with his throat and mouth. He was treated by several physicians and was hospitalized several times. The condition of his throat seemed to become worse when he was given penicillin. He had had to undergo blood transfusion several times because of the "loss of blood cells in my blood" that followed the administration of sulfonamide drugs.

In January, 1950, it had been decided that the patient's throat trouble might be due to penicillin allergy and so he was treated with aureomycin, but this also made his throat trouble much worse and he had to be hospitalized. While he was in the hospital this time, chills, fever, and bilateral pleuritic pain developed. A diagnosis of pneumonia was made, and he was treated again with sulfonamide drugs and penicillin; this treatment made the condition of his mouth much worse, but his fever subsided. He had to undergo 2 blood transfusions after this last episode. Since then he had been very tired and weak. He had continued to have intermittent mild pain in the anterior part of his chest, especially with deep breathing. He again began to run a fever and to have sweats almost every night after retiring. He had noticed mild dyspnea, but never much cough. He had experienced hemoptysis only with the episode of pneumonia. His appetite was

good and he had lost no weight. Roentgenographic examination of his chest in March 1950, was reported to have given negative results. The reaction to a tuberculin test given 4 years previously had been reported as negative and none had been done since.

On admission here it was learned that the patient occasionally noticed bright red blood on the toilet tissue after a bowel movement. A rash had developed recently on his scrotum and penis. The patient was thin but well developed, and he apparently was in no distress. He was rather pale and appeared chronically ill. In his mouth, on the lower lip and uvula, there were multiple lesions, described as "aphthous ulcers." There were large, slightly tender submental nodes. The liver was palpable 2 fingerbreadths below the costal margin and the spleen was palpable. A maculopapular rash was present in both antecubital areas and on the scrotum and penis. The blood pressure was 120/84.

While the patient was being examined at the clinic his condition suddenly became worse, and chills, fever, and a productive cough developed. Pleuritic pain recurred, and he became dyspneic. He was admitted to the hospital where his course was downhill. He became jaundiced several days before his death, and his temperature fluctuated between 99 and 100 degrees F. Bone marrow aspiration done 2 days before his death because of severe anemia disclosed, on smear, a few organisms interpreted as Histoplasma capsulatum. A pleural effusion developed several days before death, and from 2 cubic centimeters of yellow fluid obtained by thoracentesis Histoplasma capsulatum was cultured.

Laboratory examination revealed albuminuria, grade 3; erythruria, grade 2; pyuria, grade 1; and the presence of a few hyaline and granular casts. The urinary findings remained about the same throughout his stay in the hospital. Other laboratory findings were: hemoglobin, 13.2 grams; erythrocytes, 4,660,000; leucocytes, 6,300; lymphocytes, 21 per cent; monocytes, 11.5 per cent; polymorphonuclear leucocytes, 64.5 per cent; basophils, 0.5 per cent; metamyelocytes, 1 per cent; myelocytes, 1 per cent; and promyelocytes, 0.5 per cent. Over the course of 14 days the erythrocyte count fell to 2,870,000 and the leucocyte count to 3,600. The results of tests for uroporphyrin, porphobilinogen and coproporphyrin in the urine were negative. The Paunz test for amyloid gave negative results. The agglutinations for Salmonella typhosa, Salmonella paratyphi, Salmonella schottmuelleri, Pasteurella tularensis, Proteus OX19 and Brucella abortus gave negative results, as did a flocculation test for syphilis. Other data were: albumin-globulin ratio, 3.1 to 6.2; sodium, 120 milliequivalents, and potassium, 5.5 milliequivalents per liter of serum; and urea on the day of death, 207 milligrams per 100 cubic centimeters. A roentgenogram of chest on admission was read as negative, but one on the day of death was thought to show early pneumonia of right base.

Tubercle bacilli were not found in smears of sputum, urine, pleural fluid, and bone marrow. Intestinal parasites were not found in smears of the stool and malarial parasites were not found in the blood. Cultures of the urine were negative for tubercle bacilli, but positive for Histoplasma capsulatum. Cultures of the blood, pleural fluid, and bone marrow for Histoplasma capsulatum also gave positive results. Guinea-pig inoculations with bone marrow, urine, and pleural fluid did not disclose the presence of any tubercle bacilli. Culture of the blood, urine, and sputum for Brucella organisms gave negative results.

At necropsy the following anatomic diagnoses were made: (1) disseminated granulomatous disease involving the lungs, liver, spleen, bone marrow, and lymph nodes, (2) fibrous pleurisy on the right, (3) ulcer of the tongue, (4) ulcers of the esophagus, and (5) chronic pyelonephritis from histoplasmosis.

Cultures from the left lower lobe of the lung, liver, and spleen were negative for tubercle bacilli. Cultures for fungi of the spleen, liver, esophagus, lymph nodes, bone marrow, and lungs were positive for Histoplasma capsulatum. Smears from the spleen right lower lobe, and left lower lobe of the lungs were negative for tubercle bacilli.

The peritoneal cavity contained 1,500 cubic centimeters of dark red watery fluid. Numerous rubbery mesenteric nodes measuring up to 2 centimeters in diameter were palpated. The left pleural cavity contained 50 cubic centimeters of clear fluid and the right pleural cavity was obliterated.

The right lung weighed 1,095 grams and the left 1,065 grams. Both lungs were studded with myriads of soft gray nodules measuring 0.1 to 0.3 centimeter in diameter. These were seen both over the pleural surface and on the cut surface. The cut section was dark gray and extremely moist.

The spleen weighed 780 grams. The capsule was blue-gray and tense. On cut section there were multiple gray-white nodules throughout the parenchyma similar to those seen in the lungs.

The liver weighed 3,130 grams. The capsule was mottled purple and glistening. Numerous yellow-gray nodules 0.2 centimeter in diameter were seen on the capsule and on the cut surface.

Several shallow ulcers, 0.7 centimeter in diameter, with flat bases were present on the lateral and inferior surface of the tongue.

Under the capsular surface of the right adrenal gland there was 1 small yellow nodule 0.2 centimeter in diameter.

The right kidney weighed 310 grams and the left 325 grams. The capsules stripped easily. The cortex was a dark red purple while the medulla was a lighter, tan purple. A few tan nodules 0.1 centimeter in diameter were seen in the parenchyma.

The posterior wall of the bladder showed evidence of submucosal hemorrhage and edema. Several yellow nodules 0.2 centimeter in diameter were seen under the surface.

Microscopic examination of the right upper lobe of the lung disclosed, throughout the section, confluent granulomatous areas which were necrotic and

caseous at their centers, with closely packed surrounding fibrous tissue, lymphocytes, and a few giant cells. Considerable edema and numerous pigmented macrophages were observed. All 3 right lobes and the left lower lobe were similar.

On the tongue there was a superficial ulceration with the loss of squamous epithelium, slight undermining of the edges, and a flat base covered with fibrin and beginning organization. In one area there was a clump of small, oval, blue-staining nuclei in a meshwork of mycelial filaments suggestive of Candida albicans, and tissue debris. No definite cytoplasm could be distinguished.

In the spleen numerous small granulomatous areas and, under the oil immersion lens, small, oval, blue-staining bodies with a surrounding clear cytoplasm were seen. In the pancreas there were 2 granulomas with central necrosis, while in the cortex of the kidneys scattered collections of lymphocytes and connective tissue replaced the tubular epithelium. Occasionally fibrotic glomeruli were seen. In the adrenal there were scattered granulomatous areas in the cortex, and in the lymph nodes there was increase of connective tissue stroma and small granulomas were present.

CONCLUSIONS

The clinical manifestations of histoplasmosis may be quite variable. The disease may simulate tuberculosis in particular—so much so, in fact, that patients who present symptoms of pulmonary or even generalized tuberculosis but from whom tubercle bacilli cannot be isolated should undergo careful additional bacteriologic studies in an effort to isolate Histoplasma capsulatum. Even on histopathologic examination histoplasmosis may simulate tuberculosis so closely that a diagnosis should not be made by this method alone unless organisms are clearly distinguishable and even then bacteriologic methods should be used for confirmatory evidence.

Histoplasmosis is a protean disease. It may be localized or generalized and it may imitate any other granulomatous disease. The histoplasmin skin test, in our experience, has not proved useful in differential diagnosis. The disease occurs much more frequently than was previously considered, since many infections are now known to be mild and subclinical. The route of entry of the fungus is not definitely known although circumstantial evidence strongly suggests the respiratory and digestive tracts. The mode of transmission is still unknown.

Many patients who have this disease will die of it because there is no satisfactory specific therapy. Patients with isolated pulmonary lesions have an excellent chance of cure by surgical treatment.

Involvement of the adrenal glands occurs frequently in generalized histoplasmosis, and this may be the etiologic basis for some of the cases of Addison's disease. At least, histoplasmosis should be considered when a case of Addison's disease is being investigated. If, on microscopic section, spherical or oval encapsulated organisms 2 to 5 microns in diameter are seen in the cytoplasm of macrophages in a granulomatous lesion and the patient has not been in tropical areas, for all practical purposes a diagnosis of histoplasmosis may be made regardless of whether or not a positive culture has been obtained. It is important to remember that positive cultures may be obtained even though no tubercles or organisms are visible in histologic sections. We have found that Sabouraud's medium is not as satisfactory as enriched media containing antibiotics for culturing Histoplasma capsulatum.

Those patients who present an oropharyngeal lesion or have renal involvement as evidenced by albuminuria seem to have a poorer prognosis than do patients without these findings.

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THE RADICAL BREAST OPERATION

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OVER a period of many years, my associates and I have developed in our Breast Clinics what we consider to be a more extensive, complete, systematized, and precise radical mastectomy, based on five definite concepts.

These basic concepts consist of: (1) the original basic concept of Halsted and Willy Meyer which remains unaltered, i.e., a dissection beginning in the axilla and extending downward, including the nodes, the muscles, fascia, and breast en masse and in continuity; 2) a wide area of skin and fascial removal; 3) removal of the epigastric nodes; (4) removal of the 8 pathways of spread to the axillary, thoracic, and abdominal lymph basins, as well as the 5 groups of nodes, and (5) an antiseptic technique to prevent local implantation and spread from the biopsy site and from involved nodes or infiltrated areas.

Sampson Handley added concepts 2 and 3 more than 30 years ago, in his study and advocacy of his theory of direct lymphatic permeation. His third principle led to the dissection and development of wide skin flaps, as we know them today, and the extension of the incision into the epigastric triangle. To these 3 basic concepts, we have added 2 additional principles (4 and 5) and, since 1924, have extended the operation to include them.

LYMPHATICS

The basic principle underlying the surgical therapy of breast cancer is that the percentage of 5 year survivals and the duration of life of those who do not survive are inversely proportional to the percentage of node involvement.

Therefore, of prime importance and foremost consideration in the technique of radical mastectomy are the arrangement and distribution of the lymph nodes, the drainage pathways, the lymph sheds, and basins of the breast. The radical operation should be carried out in systematized, sequential, connected steps, in such a way that all pathways and nodes are assured of removal and in a manner that makes identification and counting of the nodes easily accomplished after removal.

Briefly, the lymphatics of the breast, superficial and deep, collecting and drainage, all communicate with the subareolar lymph plexus, which we call the subareolar cistern. The superficial or subcutaneous collecting lymphatics communicate with the subareolar collecting lymph vessels running beneath the breast capsule (superficial fascia) at the areolar border. Both drain into the cistern. This subareolar lymph pool communicates via the intralobular and interlobar lymphatics with the deep plexus of lymph vessels lying behind the breast and on the posterior layer of the superficial fascia (Fig. 1). All the collecting lymphatics converge to the areolar border and enter the cistern and diverge in centrifugal pathways, 5 of which enter 1 of the node groups and drain into 1 of the 3 great basins—axillary, thoracic, or abdominal (Fig. 2). The substernal pathway to the mediastinum, the transmammary, and the superficial descending abdominal pathways do not traverse any of the 5 node groups. The arrangement of the node groups (Fig. 3) is: subclavicular, 2 to 4 in number; pectoral, 2 to 4 in number; axillary, 14 to 18 in number; subscapular, 2 to 4 in number; and epigastric, 2 on each side.

These are the 5 external groups of nodes which can and must be removed in the course of every radical operation. The subclavicular, pectoral, axillary, and subscapular groups constitute the axillary basin which collects all drainage from the largest pathways and to 28 of the 34 nodes (Fig. 4). The thoracic basin consisting of the internal mammary and mediastinal nodes (not included in the figures given) has two direct pathways from the medial aspect of the breast and it is a

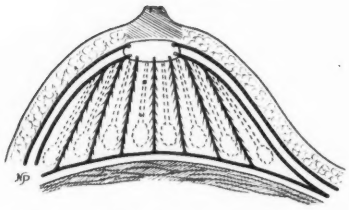

Fig. 1. Lateral view of the subareolar lymph cistern. The subcutaneous and subareolar lymphatics enter and form the cistern. The interlobular and intralobular lymphatics traversing the breast connect the deep lymphatic plexus with the cistern. (An incision into the areola enters the entire lymphatic system.)

fortunate fact indeed that lesions of the inner hemisphere of the breast constitute only 18 per cent. The abdominal basin is composed of Gerota's pathway to the epigastric nodes, directly to the subdiaphragmatic nodes and liver via the linea alba and round ligament. The interpectoral nodes (Rotter's nodes, Fig. 5), usually 2 in number, lie directly behind the breast between the pectoralis major and minor muscles and are a part of the axillary group. The lymph vessels draining into these nodes, usually 1 and occasionally 2, course directly through the breast (Groszmann's pathway) and perforate the fibers of the pectoralis major muscle to enter these nodes. This group of nodes communicates directly with the apical axillary nodes by 2 efferent pathways, 1 lateral and 1 medial to the borders of the pectoralis minor (Fig. 5).

Fig. 2. The 8 lymphatic pathways (superficial and deep): *1*, pectoral pathway to pectoral nodes, and a branch to subscapular nodes; *2*, internal mammary pathway to internal mammary nodes; *3*, Gerota's pathway to epigastric nodes and abdomen; *4*, Groszmann's pathway from Rotter's nodes to apical axillary nodes; *5*, transmammary pathway to opposite breast; *6*, substernal pathway to mediastinal nodes; *7*, subclavian pathway to subclavicular nodes; and *8*, the superficial descending abdominal pathway to abdominal wall. (All 8 pathways are completely removed during the radical operation.)

The pathways to the subclavicular, pectoral, axillary, and subscapular nodes lie within the great pectoral fascia. The transmammary pathway, Gerota's pathway to the epigastric and subdiaphragmatic nodes, and the superficial descending abdominal pathway all lie in the superficial fascia. The pathway to the internal mammary nodes runs in the superficial fascia to the lateral border of the sternum medial to the internal mammary artery and vein, thence directly to the internal mammary nodes. The substernal pathway direct to the mediastinal nodes is one of the main pathways which does not traverse any of the external groups of nodes. The internal mammary and mediastinal nodes comprising the thoracic basin are the internal node groups (Figs. 2 and 3).

The important practical technical points in this arrangement of the lymphatics are two: (1) all pathways, whether in the superficial or deep fascial planes, must be transected at only one point, the most remote perimeter of the radical dissection (sternal border, clavicle, latissimus border, epigastric triangle); and (2) in no instance, when cutting a pattern for skin flaps, should the incision be near the areolar border or deeper than the skin itself.

With these two basic considerations in mind, it will be obvious, in following the technique of the radical dissection portrayed, that no lymph channel, either collecting or drainage, superficial or deep, can possibly be transected during the operation and no spilling or implantation can occur (Fig. 4). The operation is designed and systematized in sequential steps to ensure removal of all 5 external groups of nodes and all 8 pathways in their entirety.

ANTISEPSIS

It has long been my contention, as published many times previously, that the main cause of local recurrences is the implantation of cancer cells (and/or virus) in the operative field

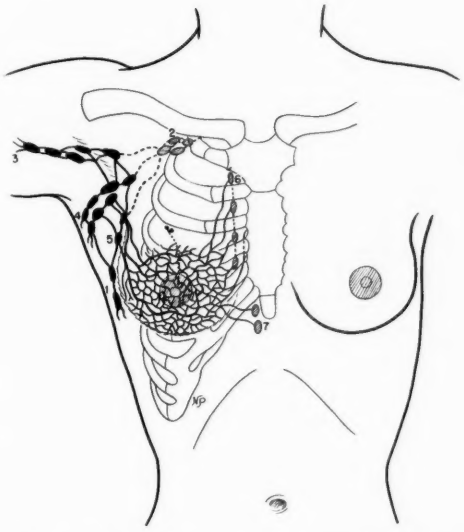

Fig. 3. The node groups: *1* and *5*, pectoral group; *2*, clavicular group; *3*, axillary group; *4*, subscapular oup; and *7*, epigastric group. (The internal mammary ain within the thorax (*6*) is also shown.) Groups *1* d *5*, *2*, *3*, *4*, and *7* and their pathways are all removed ring the radical procedure.

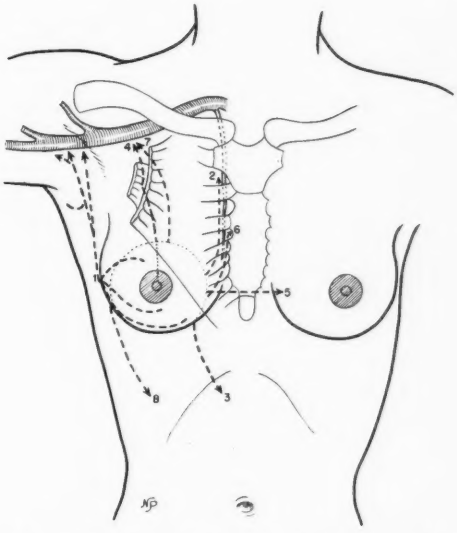

Fig. 4. The 8 lymphatic pathways, showing their relationship to breast, chest wall, and pectoral muscles. During the radical operation these pathways are severed only at the most remote perimeter of the dissection in the case of pathways *2*, *5*, and *6* and are completely removed with their node groups in the case of the other 5.

y the operator during the operation. With ne of my colleagues, a pathologist, we have lemonstrated many times the presence of can- er cells on the instruments, gloves, and in the entrifuged sediment from the basins in the perating room after biopsy. Furthermore, we have seen 2 instances of implantation of ancer into the donor site during skin grafting at the completion of the radical operation. Since 1924, we have employed an antiseptic technique throughout the course of the radical dissection, using pads saturated in antiseptic solution, a change of gowns, gloves, and instruments after biopsy, and the suture of a gauze sponge saturated in the antiseptic solution in the biopsy site. This procedure is one of the main factors which has resulted in reducing the incidence of local recurrence to less than 4 per cent.

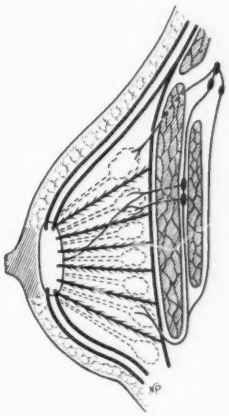

Fig. 5. Vertical sagittal section, showing Groszmann's pathway to the interpectoral (Rotter's) nodes. The subareolar cistern, formed by the junction of subcutaneous and subareolar lymphatics, is shown together with the interlobular and intralobular lymphatics connecting the deep lymphatic plexus behind the breast to the cistern. Groszmann's pathway from Rotter's nodes to axillary nodes is shown and its relationship to pectoralis major, pectoralis minor, and subclavius.

GENERAL PRINCIPLES

Based on these five concepts, certain fundamental principles must be adhered to throughout the radical dissection. The lymphatic

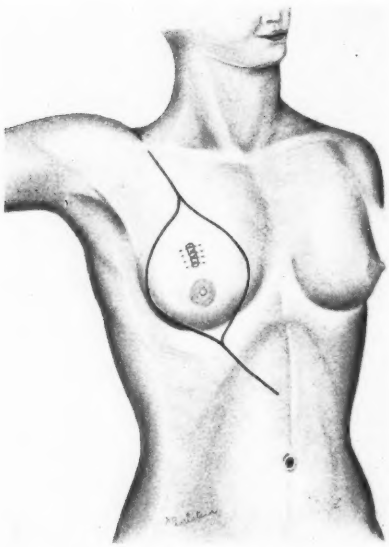

Fig. 6. The incision is begun at the coracoid and continued to the epigastric triangle just proximal to the median line affording free access to axilla, wide skin and fascial removal, and access to epigastric nodes.

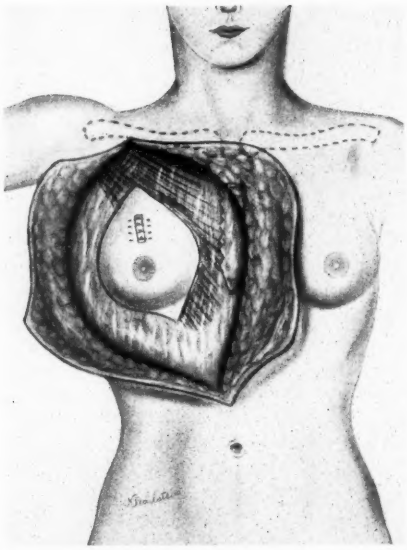

Fig. 7. The skin flaps consist of thin skin and skin only, mobilized to above the clavicle, to opposite external border, to epigastric triangle, and beyond the latissimus dorsi (layer I).

trunks should be transected only at the most remote perimeter of the field (clavicle, sternum, latissimus border, and epigastric triangle). Skin incisions must be kept wide of the areola and the subareolar lymph cistern. All dissections must avoid stripping and decapsulating lymph nodes and spilling of cancer cells (or virus). Moreover, a systematized dissection is strictly adhered to which not only includes all 8 pathways but also the removal of all 5 node groups in such a way that these nodes may readily be identified and counted after removal. Counting the nodes and recording the location of involved nodes as well as the percentage of involvement have proved of great value during the past 25 years that we have carried out this procedure, both as to prognosis and as a basis of postoperative therapy. Only once during radical dissection do lymphatic vessels cross from one plane to another. Groszmann's pathway passes directly through the breast to Rotter's nodes lying between the pectoralis major and minor muscles (the interpectoral nodes), and 2 pathways extend from these 2 nodes above and below the border of the pectoralis minor to the apical nodes of the axillary group. These trunks must be avoided in taking down the pectoralis minor from its attachment at the coracoid above. Sharp dissection only should be used. Blunt dissection has no place in the surgery of cancer and gauze dissection in the axilla is unsurgical and to be avoided. An antiseptic technique must be rigidly adhered to in order to avoid localized implantation from the biopsy site and, in advanced lesions, from infiltrated fascial spaces.

OPERATION

After the biopsy is completed and a positive pronouncement of malignancy given, 2 or 3 gauze sponges rolled together and saturated in an antiseptic solution, such as metaphen or merthiolate, are placed in the biopsy site. The skin is closed over the roll of gauze, each skin suture catching the gauze so that it cannot be displaced during the dissection. The ends of these skin sutures are left long and tied over a second roll of gauze saturated in the antiseptic. Gloves, gowns, drapes, and instru-

nents are then changed, and the skin repainted before proceeding with the radical operation.

Incision. The incision for radical mastectomy must fulfill four requirements: (a) complete an easy access to the axilla, (b) a wide area of skin and fascial removal, (c) access to the epigastric nodes, and (d) access to the terminus of all 8 pathways.

These are the four musts; the three musts are: (1) there must not be any scar in the axilla, (2) the incision must not come closer than 2 fingerbreadths from the lesion to the edge of the skin flaps, (3) the incision must be fingerbreadths from the areola. In all lesions involving the skin with dimpling and fixation, and in ulcerative lesions still primarily operable, a full handbreadth from the involved skin to the cut edge of the skin flap is the safest rule. This usually necessitates skin grafting which is always preferable to tight and skimpy skin flaps in which sloughing and local recurrence is apt to occur. In all lesions without skin fixation, edema, or ulceration flaps should and can usually be fashioned which can be closed easily and with little tension. Years ago, with the predominance of advanced lesions, skin grafting was more commonly required than in recent years when it is rarely needed. There are no definite statistical reports to show that skin grafting diminishes the incidence of local recurrence in any way. Grafting does delay postoperative therapy when required, and time is the important element in such treatment. Furthermore, we now know that it is not so much the removal of skin that counts but removal of superficial fascia. All of the lymphatics, collecting and drainage, enter and leave the breast between the 2 layers of the superficial fascia. Wide clearance of the areolar border in all variations and patterns of incisions should be planned because the superficial (subcutaneous) lymphatics communicate at the areolar border with the subareolar lymphatics beneath the breast capsule (superficial fascia) to form a network beneath the areola (the subareolar lymph cistern), and this lymph pool communicates with the intralobular and interlobular lymphatics through the breast to the deep lymph shed behind the breast. An incision at the areolar border enters the cistern and both lymph sheds (Fig. 1). This important technical fact should also be kept in mind in biopsies of central and subareolar lesions.

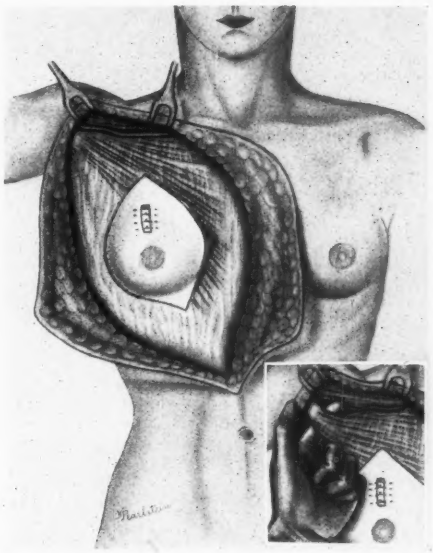

Fig. 8. Layer II consists of breast (with closed biopsy site), superficial fascia, and pectoralis major. All superficial fascia is left on pectoralis major to ensure complete removal. Cephalic vein marks division between deltoid and pectoralis major, and beginning of dissection of layer II.

The radical breast incision should begin at the coracoid (Fig. 6), palpable in the deltopectoral fossa, pass downward to the center of the superior border of the breast, from this point curve equally around the breast along its borders, if the lesion is central, to meet at a point on the inferior border of the breast directly opposite the point of its divergence at the upper border. This connected line is then extended downward and inward across the costal margin at about the ninth costal cartilage, crossing to the center of the epigastric triangle and ending just proximal to the linea alba. This incision allows flaps to be easily deflected to above the clavicle, to the sternal border of the opposite side, to the fascia of the rectus abdominis insertion below and the epigastric nodes lying upon it, and laterally beyond the border of the latissimus dorsi muscle. These

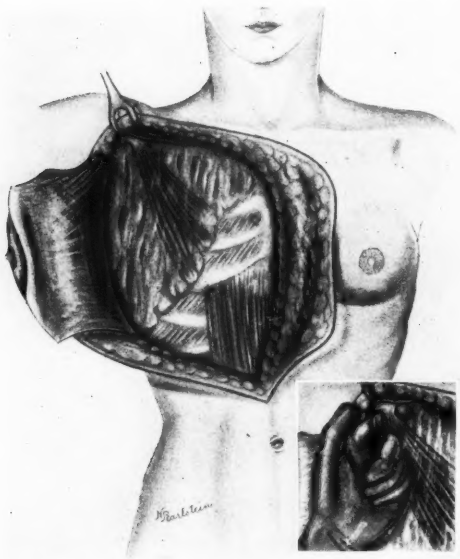

Fig. 9. Layer III consists of pectoralis minor and great pectoral fascia, pectoral (medial) and axillary (lateral) divisions. Three of the 5 node groups lie within this fascial layer. Inset shows beginning of dissection of this layer.

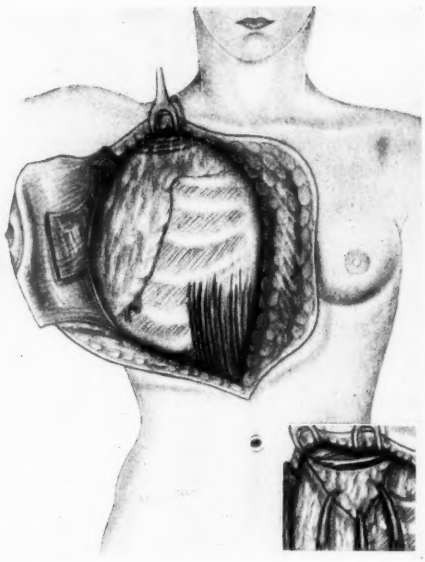

Fig. 10. Layer III (continued): pectoralis minor severed and reflected to its base. Pectoral and axillary portions of great pectoral fascia united into single fascial plane containing 3 groups of nodes. Inset, beginning dissection of layer, exposing inner cord of brachial plexus.

flaps are easily closed without tension, and the scar will lie in a straight line entirely on the anterior chest wall, well forward, with no scar in the axilla. There will be no binding of the arm nor cicatricial adherence nor fixation of the axillary vein, a common and potent cause of lymphedema of the arm. The two unchanging landmarks for this incision are: its beginning in the deltopectoral fossa over the coracoid and its ending in the epigastric triangle 1 fingerbreadth proximal to the linea alba. The two divergent lines of the incision laterally and medially may be varied in either direction according to the location of the lesion as long as a 3 fingerbreadth margin from the lesion to the edge of the remaining flap and a 2 fingerbreadth margin from the areolar border are always maintained. Lesions in the medial aspect of the breast may best be widely encompassed by a transverse ellipse, ending over the center of the sternum on its medial end and at the anterior axillary border on its lateral aspect and connected at its center point above with the usual vertical incision from the coracoid down to that point. At the center point of the lower line of the ellipse, a vertical extension is carried downward to the epigastric triangle, a pattern which we call the starfish incision. Lesions located in the high lateral region of the breast and in the axillary tail require a wide lateral sweep of the incision beginning soon after its origin at the coracoid and passing 2 fingerbreadths lateral to the areola around the breast and down to its center point below. Here it is joined by the medial limb and carried down from the point of divergence along the medial side, thus making a large medial flap to fill the wide lateral excision. In all these modifications of the radical incision, all basic principles should be observed.

Dissection of the skin flaps. In the orthodox Halsted-Willy Meyer operation, skin flaps were developed in a very limited way, 1 or 2 inches around the breast from its borders with a full thickness of skin and superficial fascia.

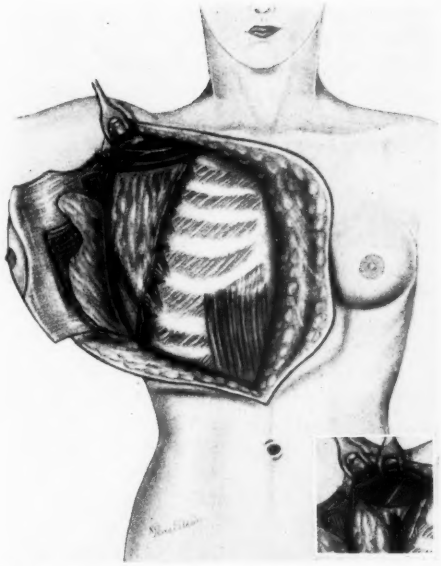

Fig. 11. Layer IV: the great pectoral fascia has been reflected to its basal attachment beyond the latissimus border. The brachial cord, axillary artery and vein, and the subscapular fascia are exposed. Inset shows beginning of dissection of this layer high in the cervicoaxillary passageway behind the axillary vessels. The thoracodorsal and the external respiratory nerve (Bell) are beginning to appear.

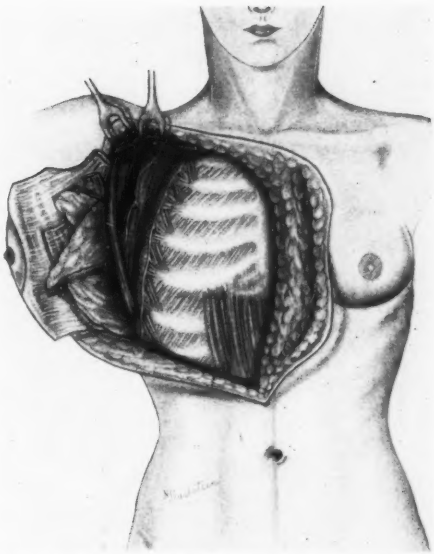

Fig. 12. Layer IV (continued): subscapular fascia is dissected downward to its base beyond the latissimus border. Thoracodorsal nerve and nerve of Bell are intact and from within out, the subscapular fascia (layer IV), the great pectoral fascia and pectoralis minor (layer III), the pectoralis major and breast (layer II) are shown freed to their joint basal attachment beyond the latissimus border.

It is now a fundamental and basic principle that these flaps consist of thin skin and skin only, with just enough fat to ensure vitality and with no superficial fascia remaining on the skin flap (the second most common cause of local recurrence). All the superficial fascia is left on the pectoralis major to ensure complete removal of this fascia. All of the collecting and drainage lymphatics enter or leave the breast between the two layers of superficial fascia and, unless this fascia is entirely removed, cancer-bearing lymph vessels will be left on the skin flaps with a high incidence of local recurrence. The skin flaps (layer I) should be mobilized well above the clavicle superiorly, to the opposite sternal border medially, well down over the epigastric triangle and rectus sheath inferiorly, and well beyond the latissimus dorsi border laterally (Fig. 7). These most distant boundaries at the perimeter of the dissection represent the point of transection of all lymphatics, both superficial and deep, at the beginning (superficial) and at the end (deep) of the dissection.

Layer II (*superficial fascia, breast, and pectoralis major*). The thin skin flaps having been completely mobilized, we now see the breast and superficial fascia lying upon the pectoralis major muscle with the site of biopsy closed over an antiseptic gauze sponge (Fig. 8). When this layer, complete with breast and pectoralis major, is dissected downward as one single layer, no lymphatics will be transected except at the most remote perimeter of the field. Beginning in the deltopectoral fossa (Fig. 8) just over the palpable coracoid, the cephalic vein lying in the groove between the deltoid and pectoralis major is visualized. When this fossa is entered bluntly, the cephalic vein and deltoid can be retracted upward and the pectoralis major separated downward and medially. In separating the clavicular portion of the pectoralis major, the thin fascial layer of the subclavicular space is found to contain

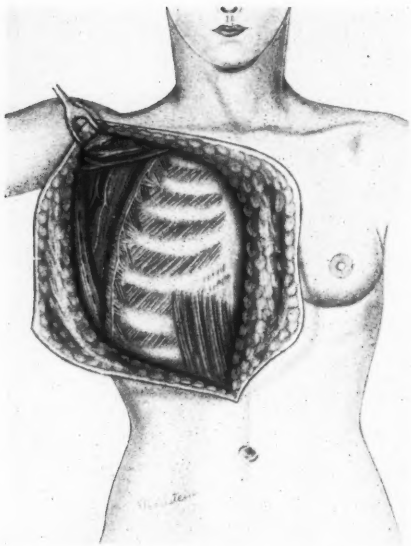

Fig. 13. The completed dissection: all 4 layers still joined at their common base beyond the border of the latissimus dorsi muscle have been removed by severance of that base (dotted line). The latissimus dorsi and subscapularis muscles, thoracodorsal nerve and external respiratory nerve of Bell, the great axillary vessels, and medial cord of the brachial plexus are shown. No lymphatic bearing fascia, superficial or deep, remains.

the external anterior thoracic artery, nerve, and vein, and the acromial branches of the acromiothoracic artery, nerve, and vein, in addition to the cephalic vein. After the lateral skin flap is mobilized well over the deltoid prominence, the insertion of the pectoralis major into the humeral groove can be easily reached, freed, and cut away as its tendinous portion enters the groove (Fig. 8, inset). The clavicular insertion is then freed after transection of the external anterior thoracic artery, nerve, and vein, and the entire muscle is reflected downward to its sternal attachment. Along the sternal border the perforating intercostal branches of the internal mammary artery and vein, usually 4 to 5 in number, are clamped, cut close to the sternal border in the second, third, fourth, and fifth intercostal spaces. Each of these vessels is accompanied by a lymphatic trunk. These perforating intercostal vessels often retract well within the external intercostal fascia and the pleura may be inadvertently punctured by clamp or needle tie. The pectoralis major is dissected down to the rectus sheath, and the superficial fascia and the rectus sheath are dissected with the pectoralis major outward to the medial border of the pectoralis minor at its lower end.

Layer III (great pectoral fascia and pectoralis minor). At this point, in order to avoid transection of Groszmann's pathway to Rotter's nodes, the pectoralis minor is mobilized by severance of its insertion into the coracoid. An incision is made at the upper end of this muscle on each side at its insertion (Fig. 9). After its coracoid insertion is cut across, the muscle is stripped out of its envelope (the great pectoral fascia) by making a linear incision along its medial border from above downward and drawing the muscle out of its envelope and deflecting it downward to its basal attachment on the third, fourth, and fifth ribs to the border of the pectoralis major, which has been left lying laterally.

As the pectoralis minor is stripped out of its fascial envelope and brought down to the border of the pectoralis major and turned outward, the great pectoral fascia is exposed as a single sheet, with its pectoral and axillary portions united (Fig. 10). This broad layer of fascia contains 3 of the 5 groups of nodes: the subclavicular, the pectoral, the axillary. This fascia (the great pectoral or clavipectoral fascia) forms the anterior sheath of the axillary vessels, envelops the subclavius, and is continuous above and behind the clavicle through the cervico axillary passageway into the neck as the pretracheal layer of the deep cervical fascia. This layer is to be dissected downward intact as a single sheet with its 3 groups of nodes, comprising about 28 of the 34 nodes which can easily be counted at the completion of the operation. Beginning in the cervicoaxillary passageway over the taut firm medial cord of the brachial plexus, which can easily be palpated and seen glistening white through the fascia (Fig. 10, inset), make an incision above and parallel to this brachial cord through the fascia and dissect it downward, ligating the acromial branch of the acromiothoracic artery and the smaller superior axillary branches above. Extend this fascial incision and cleavage laterally to the belly of the coracobrachialis, being careful

ot to remove any of the fascial covering of his muscle, thus avoiding the lymphatic channels draining the arm. Continue the division and dissection of this fascia medially to the sternal border, freeing it above and under the subclavius muscle, down over and from the axillary vein at its termination in the subclavian vein as the vein passes under the clavicle. At this point, bounded above by the subclavian vein, medially by the sternum, and inferiorly by the border of the first rib (Morenheim's space), is often found an enlarged node (Halsted node) which is the most medial of the subclavicular group and which must be brought down within this fascia. This tongue-shaped pectoral portion of the great pectoral fascia (Fig. 9) is dissected downward and outward to become mobilized with and as a part of the larger axillary portion. As this entire sheet of fascia is dissected downward and outward, the alar, the long thoracic, and thoracic branches of the acromiothoracic, as well as the medial and most lateral subscapular vessels, are ligated. The medial cord of the brachial plexus and the axillary artery and vein are bared, and along the thoracic wall the intercostothoracic nerve is severed. Care is taken to avoid removing with this layer the deeper lying subscapular fascia containing the subscapular nodes and the two large nerves, namely, the thoracodorsal nerve with its artery and vein lying over the center of the subscapular fossa and, along the thoracic wall, the external respiratory nerve of Bell which is in the medial border and boundary of this fossa. This fascial layer, the great pectoral fascia, is freed downward to its basal attachment as a single sheet with its 3 groups of nodes intact to a point well beyond the border of the latissimus dorsi, which is the termination for all layers of the entire radical dissection. During the dissection of this layer in advanced cases, with massive nodal involvement and with nodes adherent to the axillary vein, we have in 19 instances resected portions of the axillary vein with attached nodes. No harmful results and no edema of the arm arise if 1 or 2 medial and lateral vein branches, especially the most lateral, subscapular and circumflex, as well as the cephalic vein, are left intact. During

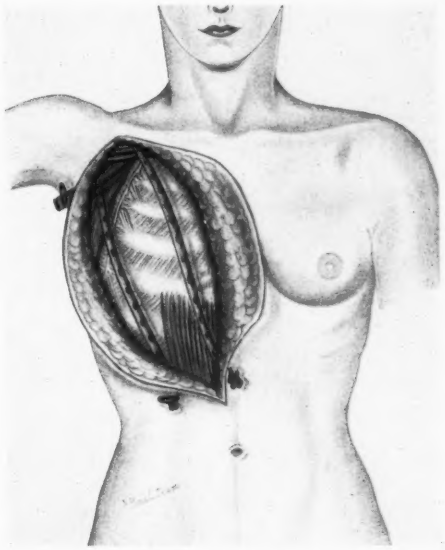

Fig. 14. The 3 drains.

the dissection of the great pectoral fascia from the apex of the axilla downward to its base beyond the latissimus border, pathways *1*, *4*, and *7* (Fig. 4) are severed behind the clavicle, and pathways *2*, *5*, and *6* at the sternal border. All the severed lymphatic vessels and nodes remain intact within the fascia as it is carried downward to the base. During this dissection, extreme care must be exercised to keep the fascial layers intact, not only to ensure removal of all nodes and to avoid severance of any lymphatic trunk, but also to avoid stripping of the capsule of any node and to prevent spilling, spreading, and implantation from infiltrated areas in the fascial planes. Strict attention to antisepsis must be observed. These safeguards apply to all of the fascial dissections, especially layer III just described, and to the next dissection (layer IV) consisting of the subscapular fascia containing group 4, the subscapular nodes.

Layer IV (*subscapular fascia*). Begin high in the cervicoaxillary passageway behind the axillary vessels, which are retracted upward, at the superior border of the scapula and dissect down the layer of fascia which covers the subscapular fossa and the belly of the sub-

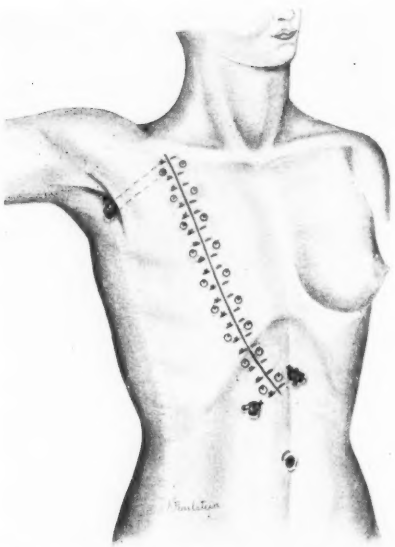

Fig. 15. The closure: the scar is entirely forward on the chest wall. No scar is present in axilla, nor binding of arm or possible adherence to axillary vein.

scapularis muscle (Fig. 11). The subscapular fascia is continuous above through the cervicoaxillary passageway with the prevertebral layer of the deep cervical fascia. It contains a group of 4 nodes, the subscapular group, and forms the posterior sheath of the axillary vessels. Separate this fascia by incising along the superior border of the scapula and then medially over the digitations of the serratus anticus along the chest wall. This medial incision exposes the long thoracic nerve of Bell lying on and supplying the digitations of the serratus anticus. Separate the medial border of this fascia along the chest wall to the scapular angle, exposing the nerve of Bell along its entire length. Beginning then above and laterally along the axillary border of the scapula, this fascial plane is brought down as a single sheet, freeing it from the anterior surface of the subscapular muscle from above downward by sharp dissection. At about the center of its width and about one-fourth of the way down from the superior border is found the middle subscapular, or thoracodorsal artery, nerve, and vein. This large nerve, which supplies the latissimus dorsi, should be conserved unless fixed by malignant infiltration. By splitting this fascial sheet downward over this nerve, it can be left intact, with its two accompanying vessels as this layer is brought downward, and the entire nerve is exposed to its insertion into the latissimus dorsi. This entire sheet is mobilized to its base lateral to the latissimus dorsi muscle with the subscapular nodes intact within it, leaving the clean belly of the subscapularis bared (Fig. 12). The lymphatic trunk entering the subscapular nodes is a single pathway which has been previously dissected down to the latissimus dorsi in layer III as one of the pectoral trunks. It enters the subscapular nodes just below the angle of the scapula and is not severed until this fascial layer (the subscapular) is severed beyond the latissimus border at the completion of the operation.

Now the entire field has been cleared of all fascia and lymphatics, leaving only the axillary artery, vein, and nerve and the medial cord of the brachial plexus, the long thoracic nerve of Bell, and the thoracodorsal nerve to the latissimus dorsi. The entire chest wall is bare and clean of all fascia and shows only the external intercostal fascia and digitations of the serratus anticus, the clean belly of the rectus abdominis below, the sternum cleared of its fascia over its anterior aspect to its opposite border, and laterally the clean muscle belly of the subcapularis (Fig. 13). The 4 layers dissected free and still joined together at the lateral latissimus border are severed at that point and removed en masse.

Drainage and closure. Adequate postoperative drainage is of paramount importance. Serum collections and clots must be strictly avoided as one of the most common causes of lymphedema of the arm. Three drains are routinely placed as follows (Fig. 14): one under the base of each flap throughout its entire length and brought out through a lateral stab at the lower end of each flap, in addition to the usual stab drain through the lateral flap into the axilla. These 3 drains keep all fossae and dead spaces empty of serum and should be removed 1 at a time, beginning with the most medial on the second day, the lateral one on the third day, and the axillary drain

n the fourth day. After the 3 drains are laced, the flaps are closed with interrupted ıtures of zytor with Davy buttons for trac- on and coaptation, and fine silk for the skin lges (Fig. 15).

Pressure should be maintained on the flaps gainst the chest wall for the first week after peration by mechanics' waste, voluminous ressings, and elastoplast adhesive. The arm not bound and daily active exercises are ıstituted the first day after operation.

SUMMARY

The main obstacle to progress in the sur- ery of breast cancer has been adherence to ıe old orthodox standard operation (Halsted-Willy Meyer) with its single basic concept.

Although that basic concept still holds good, 4 additional concepts have been added, each of prime importance, well substantiated and indispensable.

A more systematized, comprehensive technique based upon these added concepts has been described.

The recent revealing figures of Handley regarding involvement of internal mammary and supraclavicular nodes, and the 4 current experiments in the therapy of breast carcinoma (the extended radical, the McWhirter experiment, the revival of castration, and adrenalectomy) all point to the inadequacy of the standard radical operation.

What we need is better and better radical operations earlier and earlier.

THE EFFECT OF THERMAL BURNS ON WOUND HEALING

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ONE of the essential problems of the burned patient is the healing of his wounds. Since thermal injury may be followed by a number of physiologic and metabolic changes, many of which may affect wound healing, we have studied the healing of experimental laparotomy wounds in normal and burned rats.

METHODS

Adult male albino rats of the Harlan strain were used in this study. Throughout the experimental period they were fed Rockland rat diet and water ad libitum. The burns were produced under light, ether anesthesia by dipping the rats' clipped backs into water at 85 degrees centigrade for 30 seconds after the method of McCarthy. This procedure produced a third degree burn of about a third of the body surface as judged grossly and by histologic examination. The control animals were anesthetized at this time.

Twenty-four hours later, under light, ether anesthesia, the skin of the abdomen was shaved and a midline 3 centimeter laparotomy incision made in all the animals. This incision was closed with interrupted, through and through steel wire sutures placed about 0.5 centimeter apart. At various times postoperatively, animals of each group (a total of 116) were sacrificed by overdosage with ether, and the strength of their wounds tested after the method of Kobak by inflating an intra-abdominally placed condom and noting on a mercury manometer the pressure at which the incision ruptured. The sutures were removed before the tensile strength was measured. Those animals whose wounds showed gross evidences of infection were discarded.

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In another series, 92 rats were burned, wounded, and sacrificed in an identical fashion at various postoperative intervals. However, no tensile strength determinations were made. Instead, the wounds were excised immediately after death and fixed in 10 per cent formalin with the sutures still in place. After fixation, the sutures were removed and blocks were taken from the center of the wound and embedded in paraffin. Sections were cut at 6 microns and stained by a number of techniques in an attempt to gain a more accurate view of the degree and rate of healing.

The methods which were used for staining and examining the slides were modified from those used by Hunt and are described in detail elsewhere (12). The general appearance as well as the cellular features of the wounds were studied in the slides stained with hematoxylin and eosin. The reticulum (precollagen) fibers were visualized by silver impregnation (Foot's method). Collagen fibers were stained by the van Gieson technique; as the collagen fibers are formed and mature, they gradually vary in color from pale pink to brilliant red when stained by this method, while immature collagen stains uniformly yellow. The formation and state of the ground substance was followed by staining with toluidine blue. This dye stains the ground substance metachromatically (purple-red) as it appears in the granulation tissue of the wound. The intensity of this staining reaction varies inversely with the degree of polymerization of the ground substance, a more intense metachromasia being indicative of depolymerization. As wound healing progresses, the amount and staining reactivity of the ground substance gradually decrease, indicating a progressive polymerization and transformation of this material. As a rule, a healed wound contains little or no metachromatic material.

TABLE I.—EFFECT OF THERMAL BURNS ON THE DEVELOPMENT OF TENSILE STRENGTH IN LAPAROTOMY INCISIONS IN ALBINO RATS

	Burned rats				Unburned rats			
Postoperative day of sacrifice	No. of rats	Mean weight at operation, gm.	Mean weight change during healing, gm.	Mean tensile strength, mm. Hg	No. of rats	Mean weight at operation, gm.	Mean weight change during healing, gm.	Mean tensile strength, mm. Hg
2	10	310±23*	− 7±11*	30± 8.1*	10	307±23*	− 4± 6*	44±12*
3	10	295±25	−11±14	39± 3.7	10	299±21	− 7± 7	67±11
4	9	312±37	−25±16	54±11	11	301±32	−16± 8	59±13
5	11	295±25	−14±17	89±18	11	294±22	−13±13	108±25
7	9	305±40	−19±10	134±46	8	298±38	− 9±23	127±35
9	8	264±14	−21±22	169±39	8	275±19	− 7±9	>196†

*Standard deviation.
†The tensile strengths of the wounds could not be accurately determined in 3 rats in this group because the pelvic peritoneum burst before the wound ruptured.

The wound sections were examined independently by 2 observers in a uniform manner without previous knowledge of the origin of the slide. The wound area was arbitrarily defined as that limited by the epidermis and the peritoneal surface in one direction and by the width of two low power (× 35) fields on the other. Each specific histologic detail being investigated was then graded in arbitrary units (1+ to 4+) and tabulated in an attempt to obtain a quantitative evaluation of the possible changes.

RESULTS

About 10 per cent of the burned rats died in the first day following the thermal injury. Subsequent mortality during the 2 week experimental period was negligible. At about the seventh postburn day the burned skin had changed to a thick, dark crust usually without evidence of gross infection.

The burned rats lost, on the average, more weight than the control animals. This difference was more marked on days 4 and 9 (see Table I).

Gross appearance of wounds. On the second and third postoperative days, the incisions of the burned animals appeared broader than those of the controls and were covered by a dry, sanguineous exudate. Thereafter, the gross appearances of the incisions were similar.

Histologic observations. The histologic features of the healing process in the two groups are described according to the day of sacrifice, postoperatively. Despite considerable variation in the histologic appearance of the wounds among both the control and burned rats sacrificed on a given day, there were distinct differences in the rate and degree of healing in the two groups of animals.

Day 2: Two rats in each group. The wound was still open in all cases, the space being filled by serous fluid. There were a few polymorphonuclear cells and several lymphocytes. The cellular reaction was somewhat greater in the controls, one of these presenting also a few fibroblasts and a small amount of ground substance, as well as partial epithelization. The latter was minimal or absent in the other 3 cases.

Day 3: Ten rats in each group. Epithelization was well under way or complete in most animals with no significant difference noted between the two groups. In most rats the wound tract in the dermis was partially closed, the degree of closure being distinctly greater in the control animals. This was due to a greater number of fibroblasts and lymphocytes as well as to an increased amount of ground substance accompanied by early collagen formation in these rats. The fibroblasts of the burned rats were not only less numerous but also less mature, often presenting a stellate form. Similarly, capillaries and, in general, the total amount of granulation tissue appeared less abundant in this group. A moderate degree of edema was also present in the wound area of the burned animals (Figs. 1 to 4).

Day 4: Seven rats in each group. With few exceptions, epithelization of the wound was complete in all animals. No differences were detected between the two groups in amount of granulation tissue or in the degree of colla-

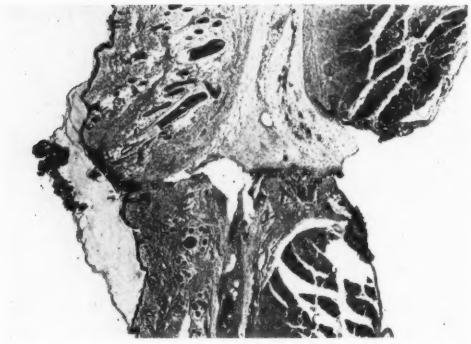

Fig. 1. LCR 22. Burned rat. Third postoperative day. The wound is closed only superficially and there is a wide gap in the central portion. Hematoxylin and eosin, ×14.

gen maturation, except that the proportion of fibrocytes to fibroblasts was somewhat smaller on the average in the burned rats than that observed in the controls.

Day 5: Two rats in each group. Epithelization was complete in the controls but in only 1 of the 2 burned rats. In these latter animals there was a distinct delay in wound healing with particular regard to the fibrocyte: fibroblast ratio and maturation of collagen fibers. The total number of fibroblasts present did not appear to be reduced when compared to that of the controls. No significant differences between the two groups were noted in the respective amounts of reticulum and metachromatic material.

Day 7: Eight rats in the burned group and 13 controls. In the burned animals, a distinctly higher incidence of infection was present. Epithelization of the wound was complete in both groups except for 2 massively infected burned animals which were discarded from the series. In general, the controls showed a smaller total number of fibroblasts and fibrocytes with a relative increase of the latter cells. Capillaries were less numerous and, in general, the granulation tissue present in the wound appeared to be somewhat less abundant in the controls than in the burned rats, possibly because of greater retraction of the wound in the former. The collagen fibers were more mature and the amount of precollagen (reticulum) was less abundant. All findings, therefore, point to a more advanced healing in the controls than in the burned rats (Figs. 5 to 8).

Day 9: Eight rats in each group. Delayed healing was again observed in the wounds of the burned rats when compared with those of the controls. This was evidenced by an increased number of mesenchymal cells and lesser maturity of the mesenchymal cells and collagen in the burned animals. The total amount of granulation tissue and the number of capillaries were also slightly greater in this group. No significant differences were noted in the epithelization and the incidence of infection between the two groups.

Day 11: Five rats in each group. Epithelization was complete in both groups. A greater incidence of infection was noted in the burned rats. Otherwise, no significant differences were observed.

Day 14: Four rats in the control and 3 in the burned group. Epithelization was complete in all rats. Granulation tissue *in toto* appeared somewhat more abundant, more vascular, and more cellular in the burned animals. Collagen maturation was also less advanced in the same group. The lag in healing, however, was not as marked as that seen at day 7 (Figs. 9 to 12).

Tensile strength measurements. On days 2 and 3, the wounds of the burned rats ruptured at a significantly lower pressure than did those of the controls (Table I and Fig. 13). No sta-

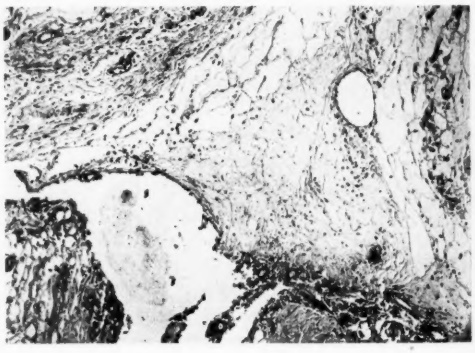

Fig. 2. LCR 22. Burned rat. Third postoperative day. Detail of Figure 1. Note the serofibrinous edema of the wound's edge with minimal fibroblastic proliferation (right lower corner). Hematoxylin and eosin, ×53.

istically significant difference between the verage tensile strengths of the wounds of the wo groups of rats was observed on days 4, 5, nd 7. On the ninth postoperative day, the ounds of the burned animals were, on the verage, weaker than those of the unburned roup. However, it is not possible to deter- nine with certainty whether this difference is ignificant, since the pelvic peritoneum burst n 3 of the control animals before the laparot- my wounds ruptured and the exact strengths f the wounds were not determined in these nstances. Because of the increasing inaccu- acies of the determinations in the later stages f healing, no tensile strength measurements ere made after day 9.

DISCUSSION

In the present study, the healing of laparot- my wounds in the burned rats was signifi- antly different from that in the unburned ontrols. Epithelization was not affected, but here was a definite delay in the formation of ranulation tissue in the incisional wounds of he burned animals with a lag in the appear- nce and maturation of the fibroblasts and he ground substance. The eventual number nd amount of these two elements, however, lid not appear to be affected, and abundant granulation formed in the wounds of the burn- ed rats in time. In some of the burned rats the wound area appeared somewhat more edematous than that of the controls. The in-

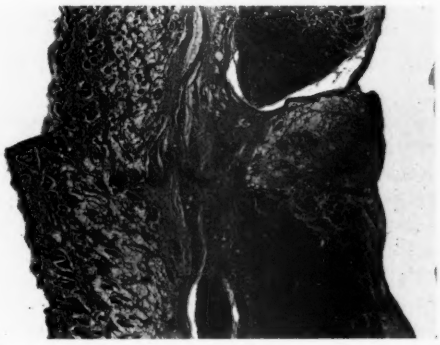

Fig. 3. LCR 25. Control rat. Third postoperative day. The wound is almost completely closed. Fairly abundant granulation tissue is present in the central segment of the wound. Note a small stitch abscess in the lower half of the field. Hematoxylin and eosin, ×14.

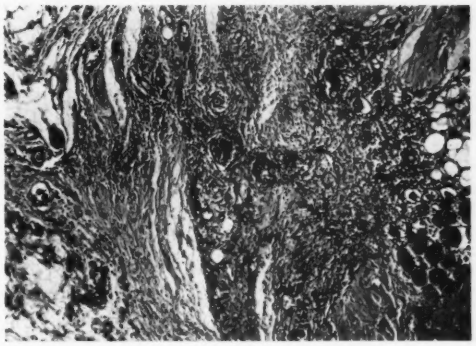

Fig. 4. LCR 25. Control rat. Third postoperative day. Detail of Figure 3 demonstrating numerous fibroblasts and capillaries in the granulation tissue. Hematoxylin and eosin, ×53.

cidence of wound infection was also somewhat higher among the burned animals. The differences between the two groups were, in general, less marked late in the postoperative period and it is likely that 3 or 4 weeks following the operation the scars would have been essentially similar. A consistent observation in both groups was that the granulation tissue adjacent to the epidermis matured earlier than that deeper in the wound. This may be due to a better approximation of the wound edges near the surface and may have been a factor in determining the speed of epithelization which as a rule was complete by the fifth postoperative day.

There are many factors which may have influenced the healing of wounds in the burned animals. During the first few days of healing, the strength of incisional wounds may be largely dependent on the inflammatory clot. Following severe thermal injury and shock, there may be profound alterations in the clotting mechanism; fibrinogen and prothrombin concentrations may fall and fibrinolysis may appear. It is possible that such changes may be, in part, the basis for the significantly lowered tensile strength of the laparotomy wounds of the burned animals on days 2 and 3. In keeping with this possibility is the observation that on the second and third postoperative days the incisions of the burned animals appeared broader than those of the controls and were covered by a dry, sanguineous exudate.

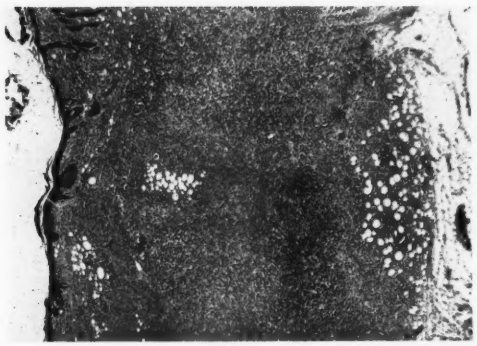

Fig. 5.

Fig. 7.

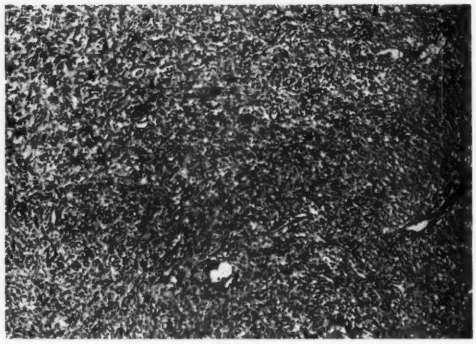

Fig. 6.

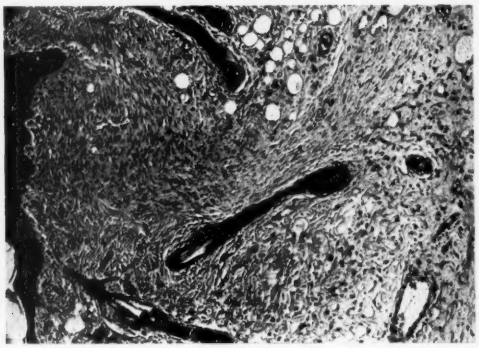

Fig. 8.

Fig. 5. LWR 26. Burned rat. Seventh postoperative day. The wound is seen to be completely closed by abundant and cellular granulation tissue. Hematoxylin and eosin, ×14.

Fig. 6. LWR 26. Burned rat. Seventh postoperative day. Detail of Figure 5 showing abundant vascularization and numerous lymphocytes and fibroblasts. Only few mature fibrocytes and collagen fibers can be distinguished. Hematoxylin and eosin, ×53.

Fig. 7. LWR 28. Control rat. Seventh postoperative day. Wound is completely closed, scar tissue appearing particularly dense in outer half. Note omental adhesions undergoing organization. Hematoxylin and eosin, ×14.

Fig. 8. LWR 28. Control rat. Seventh postoperative day. Detail of Figure 7. Scar tissue contains many fibroblasts and fibrocytes with parallel arrangement to wound surface. Collagen fibers appear well formed. Only a few capillaries are present. Hematoxylin and eosin, ×53.

Extensive deep thermal trauma is followed by marked nutritional disturbances, and it has long been known that many different nutrients may affect wound healing. Among the best known of these are the effects of protein deficiency. Prolongation of the lag period, delay in epithelization, delay in proliferation and maturation of connective tissue and an increase in wound edema and infection have been observed in protein-deficient animals and patients. These changes are similar to those observed in the wounds of the burned animals in the present study.

Following burns, there is an increased urinary excretion of nitrogenous products in patients and animals. This increased nitrogen excretion begins very shortly after the onset of trauma, reaches its peak during the first week, and persists from 2 to 6 weeks. In general, the metabolic abnormality is related to the severity of the burn and the status of the individual (age, sex, and nutrition) at the time of injury. The greatest losses of nitrogen have been demonstrated in cases of the severely burned, previously well nourished, young adult male.

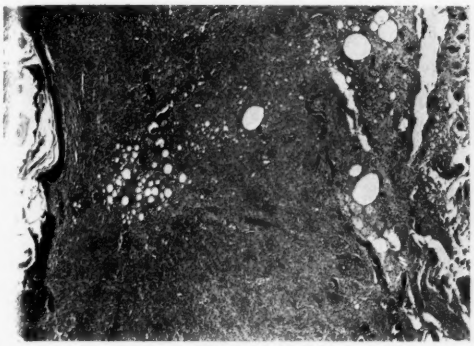

Fig. 9.

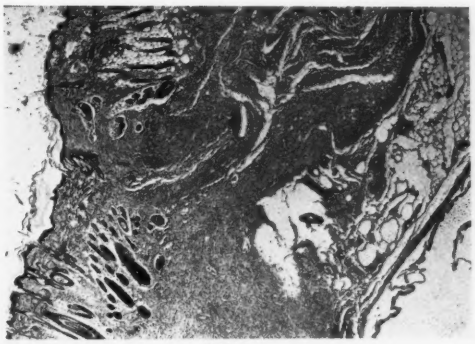

Fig. 11.

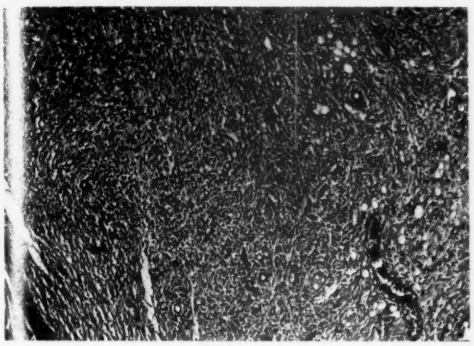

Fig. 10.

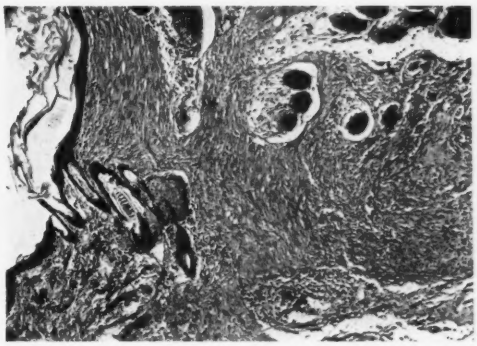

Fig. 12.

Fig. 9. LWR 64. Burned rat. Fourteenth postoperative day. Note abundant and fairly cellular granulation tissue through wound area, organized omental adhesions at right. A small crust with superficial infection interrupts continuity of epithelization. Hematoxylin and eosin, ×14.

Fig. 10. LWR 64. Burned rat. Fourteenth postoperative day. Detail of Figure 9. Numerous fibroblasts, lymphocytes, and capillaries are still present in the granulation tissue. Hematoxylin and eosin, ×53.

Fig. 11. LWR 68. Control rat. Fourteenth postoperative day. The wound is closed by dense scar tissue throughout. Omental adhesions can be seen at right. Hematoxylin and eosin, ×14.

Fig. 12. LWR 68. Control rat. Fourteenth postoperative day. Detail of Figure 11. The scar tissue consists of dense collagen containing relatively few fibroblasts and fibrocytes aligned parallel to the surface. Only occasional capillaries can be seen. Hematoxylin and eosin, ×53.

It has been suggested that one of the purposes of the metabolic reaction to injury reflected in the increased nitrogen excretion is to provide the wounded area with the building blocks necessary for tissue repair. The observations of Sandblom and Young and associates that secondary wounds heal faster than primary wounds have been cited in support of the theory. However, the initial wounds made in these studies were small, and it is questionable whether a period of significant metabolic imbalance occurred. Further, Taffel, Donovan, and Lapinski have recently reported contrary findings. In their study, young growing white rats, each weighing about 100 grams, were used. In the experimental animals, a 4 centimeter incision was made (and immediately closed) under ether anesthesia through the skin, subcutaneous tissue, and muscle in the interscapular area. Five or 15 days later, a 1 centimeter incision was made under ether anesthesia through the wall of the cardia of the stomach and closed with a single layer of No. 000 plain catgut. The control animals were subjected to the same regime, including the 2 administrations

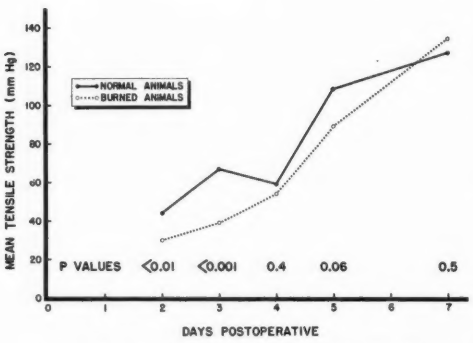

Fig. 13. The effect of thermal burns on the development of tensile strength of abdominal wounds in young adult male albino rats.

of ether anesthesia, except for the making of the primary wound on the back. There were no significant differences in the histologic appearances or tensile strengths of the stomach wounds among the various control and experimental groups. The degree of metabolic disturbance produced by the initial wound is not known since no biochemical measurements were made. It was assuredly less than that produced by the extensive deep thermal burn employed in the present study.

Early after burns there is a very brief period of hypoproteinemia, followed quickly by transitory hypoproteinemia, due to shifts and losses of water, electrolytes, and plasma proteins. Later, consequent to a continued and prolonged period of negative nitrogen balance, the hypoproteinemia may persist and progress as part of a generalized tissue protein deficiency.

Since wound repair involves the proliferation of cellular and intercellular protein elements, it is not surprising that wound healing is impaired in the presence of protein deficiency. Further, decreased resistance to infection and tissue edema, which at times accompany protein deficiency, may delay the healing of wounds. The ill effects of wound infection on healing are well documented. Inadequate data are available in regard to the effect of tissue edema per se in regard to wound healing. It appears that the delayed wound healing characteristic of protein deficiency is further impaired when significant edema is also present. Findlay and Howes have recently studied the effect of local edema produced by external venous obstruction on wound healing in rabbits without systemic protein depletion. When edema was marked, wound healing was poor; sutures untied, broke, or pulled through; the wound edges did not agglutinate; and there was chronic seepage of interstitial fluid and lymph. When the local edema was less, wound healing was per primam, and when tested on the sixth postoperative day, the wounds in the edematous area were either as strong or stronger and exhibited more abundant fibroplasia than the wounds in the control area.

The possibility was suggested a number of years ago that a disturbance in the metabolism of one or more of the essential amino acids is one of the important factors in the pathogenesis of the increased urinary excretion of nitrogen following injury. However, there are no conclusive data substantiating this viewpoint. Croft and Peters compared the nitrogen excretion of burned rats on a 14 per cent protein diet with the excretion of those given a supplement of methionine. They found that the urinary nitrogen excretion of methionine-supplemented animals (but not cysteine or alanine supplemented animals) was significantly lower following the burn than that of the nonsupplemented group. In contrast, neither workers in this same laboratory (4) nor Chanutin and Ludewig, nor Sellers and Best nor Meyer and associates were able to confirm the nitrogen effect of methionine under similar conditions. However, Sellers and Best did find that when a methionine deficiency existed in the basal diet previous to the burn, methionine supplementation after the burn did lower the nitrogen excretion seen after injury.

Further investigation of specific amino acid metabolism following trauma is indicated from the point of view of possible influence on wound healing. Supplementation of a low protein diet by tryptophane, valine, and lysine had no apparent effect on the healing of open wounds in rats according to Morris and associates. However, the authors believed that the number of animals studied was too small

to attach any significant weight to these observations. Localio, Morgan, and Hinton reported a shift of the curve of wound healing toward normal in protein-deficient rats given a daily supplement of 150 milligrams of dl-methionine subcutaneously. Similar observations were later reported by Williamson and his co-workers for methionine (17) and cystine (16). Histologic confirmation of the beneficial effects of methionine on wound healing in rats, on a protein deficient diet, has been recently obtained by Perez-Tamayo and Ihnen. The mechanism of action of the sulfur-containing amino acids on wound healing has not been elucidated. It has been suggested that these amino acids may increase the rate of utilization of available protein by connective tissue. It has also been suggested that the sulfur-containing amino acids are preferentially utilized at the local area of wound healing as either sulfydryl radicles or as sulfate. In this regard, granulation tissue has been found to have a high sulfur content. More recently, it has been shown that wounded rats injected with S^{35} tagged l-methionine accumulate the radioactive sulfur in the wound tissue, mainly as cystine-S^{35}. This occurs even when the S^{35} content of other tissues is decreasing.

Among other nutritional factors known to influence wound healing are certain of the vitamins, particularly ascorbic acid. Following burns, there is a derangement in the metabolism of some of the water-soluble vitamins, e.g., an abrupt and sustained decrease in urinary excretion and "saturation" of ascorbic acid, riboflavin, thiamine, and nicotinamide in patients. Similar studies have not been made in burned rats. It is not known, for example, whether the rat, which can meet its normal requirements for ascorbic acid by synthesis, can do so during the period of stress following thermal injury. In this regard, it may be mentioned that the changes in wound healing observed in the burned animals are not typical of ascorbic acid deficiency.

Among the other metabolic sequelae of thermal injury are changes in hormonal activity. The majority of studies have been concerned with the adrenals. There is ample evidence to indicate an increase in adrenal activity following injury, for example, there is an early increased urinary excretion of 17-ketosteroids followed by an increased excretion of 11-oxysteroids. The possibility must be considered that adrenocortical hormones liberated in excessive amounts through the "alarm reaction" mechanism may be partially responsible for the connective tissue changes seen in the wounds of the burned animals.

SUMMARY

1. The healing of experimental laparotomy wounds was studied in normal and severely burned rats. Observations of the gross appearances, tensile strengths, and histologic features of the incisions were made.

2. The healing of the laparotomy wounds in the burned animals was significantly different from that in the unburned controls. Epithelization was not affected, but there was a definite delay in the formation of granulation tissue in the incisional wounds of the burned animals with a lag in the appearance and maturation of the fibroblasts and intercellular substances. The eventual number and amount of these elements, however, did not appear to be affected, and abundant granulation tissue formed in the wounds of the burned rats in time.

3. Some of the factors which may have influenced the healing of wounds in the burned animals were discussed.

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EXPERIMENTAL STUDIES CONCERNING FACTORS IN THE PATHOGENESIS OF ACUTE PANCREATITIS

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ALTHOUGH extensive clinical and experimental studies have been carried out to discover the pathogenesis of acute pancreatitis, agreement as to the factors contributing to the production of this condition is still lacking. The purpose of this study was to re-examine certain factors which presumably are involved in the production of the disease.

The literature on this subject is vast and controversial. A recent review was published by Ivy and Gibbs. It has been the experience of many investigators that the most consistent experimental method for the production of severe acute pancreatitis with necrosis and hemorrhage is the injection of bile or certain other irritating substances under pressure into the pancreatic duct. This method has been criticized because the pressure used was probably higher than that which obtains physiologically.

Whether a common channel between the common bile and pancreatic ducts is important in the pathogenesis of acute pancreatitis also has been the subject of much investigation and the actual role of such a channel is not unanimously agreed upon as yet. In recent years, experimental studies have indicated that obstruction of the pancreatic duct by itself results in fat necrosis and inflammatory changes in the pancreas without pancreatic parenchymal necrosis. If obstruction of the pancreatic duct in such instances was temporarily associated with pancreatic ischemia, then pancreatic necrosis, often hemorrhagic in type, would be added to the changes produced by obstruction of the duct alone. Stimulation of the external secretion of the pancreas by secretin, food and other agents, in addition to obstruction of the pancreatic duct, apparently results in a more severe degree of pancreatic edema and damage. However, according to Popper and associates (9, 11), even with the combination of stimulation of pancreatic secretion and obstruction of the pancreatic duct, pancreatic necrosis does not occur.

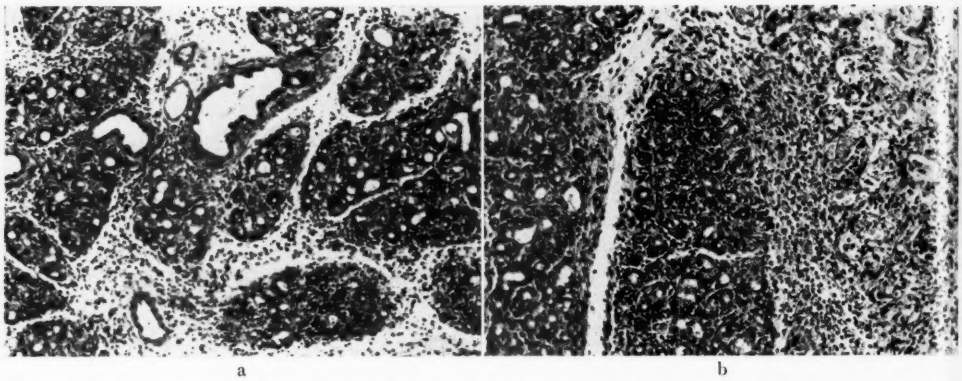
The possibility that acute pancreatitis may be produced by certain toxic substances such as alcohol has always existed. However, it appears doubtful that toxic substances, acting directly on the pancreas, play an important role in the production of acute pancreatitis clinically. Farber and Popper found that ethionine will produce pancreatic lesions, even though these lesions are not strictly comparable to pancreatitis in human beings, which fact brings up the question of certain amino-acid deficiencies in the production of pancreatic lesions.

The possibility that in certain cases acute pancreatitis might be solely the result of interference with the blood supply to the pancreas has been suggested, especially in view of the fact that acute pancreatitis occasionally occurs early postoperatively after abdominal surgery. Smyth was able to produce localized areas of acute pancreatic necrosis experimentally by injecting mercury droplets into the arterial supply of the pancreas, but a spreading type of acute pancreatic necrosis could not be produced in this manner. Although the role played by infection received considerable attention in literature in the past, this factor has not received much attention in current investigations on the origin of pancreatitis.

METHODS

The albino rat was selected for these studies for the following reasons: (1) anatomically, the external secretion of the pancreas enters into the common duct of the rat by way of many small ducts, thus permitting study of the theory of the common channel as an etiologic factor, (2) the changes in the pancreas

From the Sections of Physiology and of Pathologic Anatomy, Mayo Clinic and Mayo Foundation.



a b

Fig. 1. Partial obstruction of the common bile duct at the duodenum and ligation and division of the common bile duct at the hilus of the liver: a, dilation of acini and ducts, interlobular edema and mononuclear leucocytes (hematoxylin and eosin, ×75); b, same as in a, plus a region of parenchymal necrosis (hematoxylin and eosin, ×115).

of the rat after occlusion of the pancreatic duct appeared to be more marked than in other species, as, for example, the dog, and (3) use of the rat makes it possible to carry out effectively large numbers of experiments.

One disadvantage associated with this species is that to obstruct the pancreatic ducts, it is necessary to obstruct the common bile duct, since the rat has numerous small pancreatic ducts entering the common duct, instead of one or a few. Thus, obstruction of the common duct necessarily meant that hepatic changes and jaundice were produced which prevented the experimental preparation from being an ideal one. However, all the studies were of only a few days' duration and separate experiments indicate that obstruction of the common duct only at the hilus of the liver of the rat does not produce any significant changes in the pancreas during the period which our studies covered. The absence of a gallbladder in the rat also may be an undesirable feature in the use of the rat for these experiments, but it did not seem to be unduly objectionable.

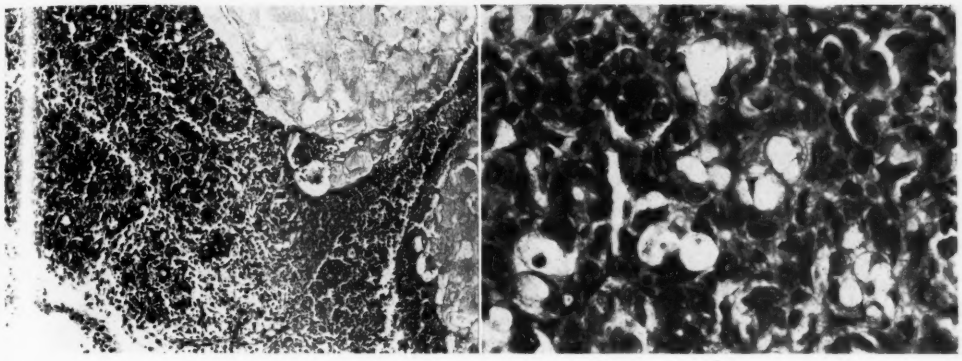
White rats weighing 180 to 380 grams were anesthetized with ether, and the common bile duct was isolated at its entrance into the duodenum or at the hilus of the liver at the point of its formation by the union of hepatic ducts, or at both locations, as the individual experiment dictated. The duct at one or both of these points was then treated as desired, by (1) partial occlusion of the duct at its entrance into the duodenum by tying fine silk over a No. 22, 23, or 27 gauge needle stylet, with or without double ligation of the duct at the hilus of the liver, (2) complete occlusion by double ligation at one or both points, or (3) complete occlusion by double ligation and transection at one or both points. It was not necessary to manipulate the pancreatic ducts directly in these procedures.

In those experiments designed for producing ischemia of the pancreas, different degrees of severity of ischemia were produced by varying the extent of reduction of circulation. Variations ranged from ligation of only the superior and inferior pancreaticoduodenal arteries at their origins to complete devascularization of portions of the body and tail of the pancreas; these latter experiments entailed splenectomy also.

A total of 72 experiments were carried out. At the termination of each experiment 1 day to 5 days after the procedures on the pancreatic ducts or vessels, gross changes were noted and specimens of pancreatic and hepatic tissue and areas of fat necrosis were placed in a 10 per cent solution of formalin for fixation. Sections were later stained with hematoxylin and eosin for histologic study.

RESULTS

Experiments designed to obstruct the pancreatic duct. In general, whenever obstruction to



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g. 2. Complete ligation of the common bile duct at th duodenum and complete ligation with division of the co mon bile duct at the hilus of liver: a, parenchymal and fat necrosis with exudative reaction (polymorphonuclear cells) (hematoxylin and eosin. ×75); b, hydropic degeneration of acinar cells (hematoxylin and eosin, ×455).

th flow of pancreatic juice was produced, the gr s changes consisted of pancreatic edema an varying degrees of fat necrosis in the re on of the pancreas and throughout the ab omen. Fat necrosis was nearly always pr ent and was often very extensive, involving large portions of the mesentery and retroperitoneal areas. However, the extent and se rity of changes varied much with different an nals, but definitely progressed with time. Hi tologic examination of the pancreas disclo ed dilatation of the ducts and acini, edema with infiltration, predominantly interlobular, of lymphocytes, monocytes, and a few polymorphonuclear leucocytes, atrophy and degenerative changes of the acini, and intrapancreatic and extrapancreatic fat necrosis (Figs. 1 to 3). The severity of the lesions in different parts of the pancreas varied. A few mitotic figures in the acinar cells were noted. Tissues taken during the later periods of this study showed fibroblastic proliferation and connective tissue formation in the pancreas. Pancreatic parenchymal necrosis and hemorrhage occurred infrequently. A total of 31 experiments were performed in this part of the study.

The question arose as to whether pancreatic changes would be magnified by partial inter-

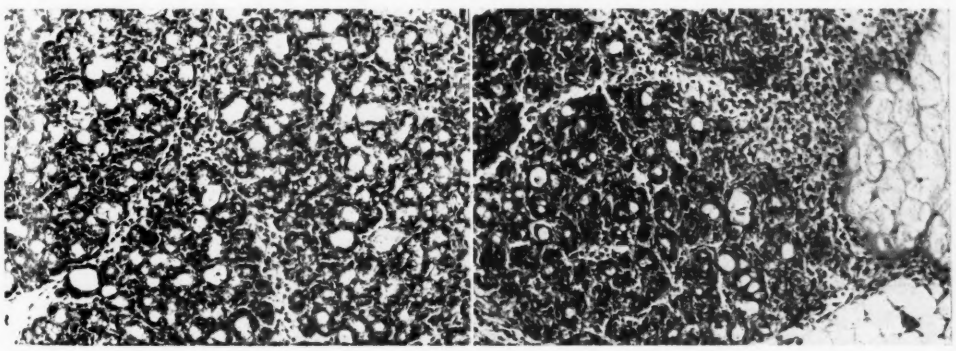

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Fig. 3. Complete ligation of the common bile duct at the duodenum and ligation with division of the common bile duct immediately below the liver (aseptic operation): a, severe dilatation of the acini similar to that observed in fibrocystic disease of the pancreas in children (hematoxylin and eosin, ×115); b, focus of parenchymal and fat necrosis with exudative reaction (hematoxylin and eosin, ×115).

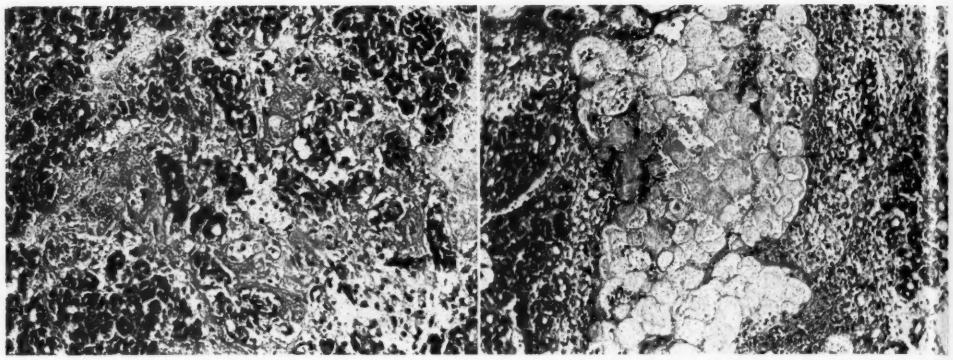

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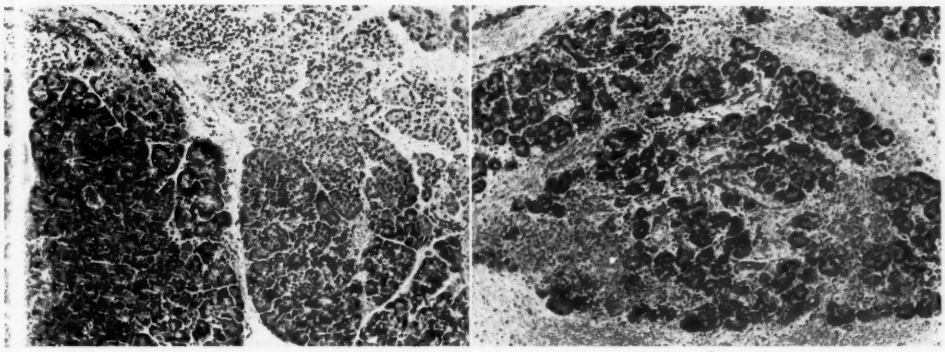
Fig. 4. Ischemia plus occlusion of the pancreatic duct: a, occlusion of the superior and inferior pancreaticoduodenal arteries for 15 minutes and complete ligation of the common bile duct at the duodenum and also immediately below the liver: note destruction of acini and severe interlobular edema (hematoxylin and eosin, ×115); b, complete ligation of the superior pancreaticoduodenal artery and of the common duct at the duodenum and also immediately below the liver: note parenchymal necrosis and exudative reaction (hematoxylin and eosin, ×115).

ference of flow from the pancreatic ducts instead of complete obstruction to flow. This was predicated on the possibility that the flow of pancreatic juice might continue in larger volume and over a longer period if the flow was only partially obstructed, rather than completely blocked. Therefore, 7 experiments were carried out in which the common duct was partially obstructed only at the duodenum, but completely divided between ligatures at the hilus of the liver (Fig. 1). Three experiments were carried out in which the common duct was divided between ligatures at both locations. No difference in the changes in the pancreas was discernible in tissue taken from rats in which complete obstruction to flow from the pancreatic ducts was produced, and tissue from rats in which only partial obstruction of the pancreatic ducts was produced.

Additional experiments in which the common duct was either partially or completely occluded at its entrance into the duodenum were done to determine whether or not the possibility of free flow of bile into the pancreatic ducts would exaggerate the changes in the pancreas. The changes so produced in the pancreas could not be distinguished from those resulting from occlusion of the common bile duct, both at the duodenum and immediately below the liver, in such a manner that admixture of pancreatic and bile juices was prevented.

Inasmuch as these experiments were carried out in the usual manner on rats without any special sterile precautions, 8 other experiments were performed in which aseptic technique was used. In 4 of these animals the common duct was completely occluded at the duodenum, and in another 4 the duct was completely occluded, both at its entrance into the duodenum and at the hilus of the liver. No difference in the changes produced could be detected between those animals in which procedures had been done aseptically and those in which procedures had been done in the usual manner (Fig. 3).

It was observed that the changes in the pancreas and the severity of fat necrosis after obstruction to the flow of pancreatic juice appeared much more marked in the rat than we had previously observed in similar experiments on dogs. During an equivalent period only a mild-to-moderate degree of edema with only a mild infiltration of inflammatory type cells and only a few small flecks of fat necrosis were observed after occlusion of all identifiable pancreatic ducts in the dog. The question arose as to whether this might be related to the fact that the rats ate at frequent intervals at all times, whereas the dogs ate only at certain times. Therefore, in additional rats, food was restricted for 24 hours prior and for 3 days subsequent to complete occlusion of the com-



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g. 5. Ischemia alone (devascularization of large areas of ncreas): a, ischemic infarction of lobules and portions of lobules; b, focal necrosis of acini with edema, hemorrhage, and leucocytic reaction (hematoxylin and eosin, ×80).

m n bile duct at the hilus of the liver and adja nt to the duodenum or adjacent to the duod num alone. The resultant changes in the pa creas of these animals could not be distin guished from changes in animals which had be n permitted to eat when they wished.

'xperiments designed to assess the effect of isc emia on the pancreas. Ischemia plus occlu ion of the pancreatic duct.—Inasmuch as pa creatic parenchymal necrosis and hemorrha ge were not observed frequently after obstr ction to the flow of pancreatic juice alone, the addition of varying degrees of temporary and permanent pancreatic ischemia was produced in 15 animals. In these studies pancreatic parenchymal necrosis of varying degrees of severity and extent usually was added to the changes previously enumerated as occurring after effective occlusion of the pancreatic ducts (Fig. 4). After ligation of the pancreaticoduodenal arteries, the areas of necrosis were usually small and scattered; after interference with arterial flow of greater magnitude, the areas of necrosis were larger. After occlusion of pancreaticoduodenal arteries for only 15 minutes, the necrosis seemed less marked and extensive than after permanent occlusion, but areas of hemorrhage appeared more often and were more severe (Fig. 4).

Pancreatic ischemia alone.—Occlusion of arterial vessels to the pancreas without interference with the flow of the external secretion of the pancreas was studied in 11 rats. Temporary or permanent occlusion of the pancreaticoduodenal arteries alone did not produce a very marked effect. Occasional foci of parenchymal necrosis with the infiltration of a few lymphocytes, monocytes, and polymorphonuclear leucocytes were observed. Otherwise, the pancreas appeared normal. More extensive devascularization of the pancreas by occlusion of more of its arterial supply, however, resulted in marked changes including necrosis, interlobular and intralobular edema, infiltration of monocytes, lymphocytes, and polymorphonuclear leucocytes, some proliferation of fibroblasts, and fat necrosis within the pancreas and, to varying degrees, throughout the abdomen (Fig. 5). Generally, these histologic changes were found in association with local ischemic infarcts (Fig. 5a). Dilatation of the ducts and acini were not observed, however. Of 8 animals in which a half or more of the pancreas was devascularized by ligation of its arterial supply, 5 died or appeared to be in extremis at the time of examination.

Experiments designed to stimulate secretion of pancreatic juice. In addition to complete occlusion of the common bile duct at both its entrance into the duodenum and the hilus of the liver, a total of 10 rats were also studied either after they had been injected frequently and subcutaneously with acetylcholine, or after they had received frequently 50 per cent solutions of ethyl alcohol by gavage or frequent doses of 0.5 per cent solution of hydrochloric acid by gavage. The resulting changes in the pancreas did not appear to be definitely

more severe as a result of the administration of these materials. Pancreatic necrosis was not observed; however, in 1 animal given hydrochloric acid, small foci of necrosis and hemorrhage were noted.

CHANGES IN THE LIVER

The microscopic changes noted in the liver in these experiments consisted of periportal accumulations of monocytes with a few polymorphonuclear leucocytes, degenerative changes in scattered hepatic cells, and the presence of numerous mitotic figures in the parenchymal cells. Occasionally, cholangitis and pericholangitis were present.

The consistent presence of the numerous mitotic figures in the hepatic cells was of interest and has been noted by other investigators after acute injury to the liver and during the same time interval as was employed in this study. We also have noted a similar occurrence in the kidney after ureteral occlusion. An increased number of mitotic figures also was present in the parenchymal cells of the pancreas after effective occlusion of the pancreatic ducts, but these mitoses were not numerous.

COMMENT

The data obtained in this study support, in general, the concepts derived by other investigators concerning the pathogenesis of acute pancreatitis. Acute obstruction of the pancreatic ducts will result in at least one form of acute pancreatitis, with peripancreatic fat necrosis, but parenchymal necrosis is generally absent. Degenerative changes and atrophy of the acinar cells occur, but necrosis usually does not. The production of a common channel between the bile and pancreatic ducts does not appear to modify the changes significantly. In earlier studies in which a common channel between the bile and pancreatic ducts was produced in goats, Mann and Giordano were unable to produce pancreatitis. However, Bisgard and Baker, working with young animals, reported the production of pancreatitis in similar experiments on goats. It appears that a form of acute pancreatitis in which necrosis is absent can be produced whenever the pancreatic ducts are obstructed, whether communication between the pancreatic ducts and bile ducts exists or not. It is well known that the injection of bile under pressure into the pancreatic duct will produce acute pancreatitis with parenchymal necrosis, but the pressures necessary are higher than those which can exist physiologically. Ivy and Gibbs concluded from a review of the literature that reflux of bile is not necessary for the genesis of acute pancreatitis.

If ischemia is added to obstruction of the pancreatic duct, parenchymal necrosis is produced in addition to other pancreatic damage. This will vary in severity depending on the degree and extent of arterial occlusion. Hemorrhage accompanies the necrosis in some instances, especially if the ischemia is temporary. Results of these studies on the pancreas are in certain respects similar to those of Thomas and Womack, in which it was demonstrated that to produce acute gangrenous cholecystitis the factors of obstruction of the duct, presence of certain chemicals and ischemia all are necessary.

We have also been able to demonstrate that in the rat acute pancreatitis with fat necrosis and parenchymal necrosis can be produced by severe and extensive pancreatic ischemia alone. Generally, however, these lesions have the appearance of focal ischemic infarcts, and do not duplicate the histologic appearance of diffuse pancreatitis observed in man. Dilatation of the ducts and acini is absent in these specimens. Evidently, fat necrosis can result independently from either severe pancreatic ischemia or obstruction of the pancreatic duct. This was noted by other workers.

The question of the relationship of vascular disease to acute hemorrhagic pancreatitis is one that is frequently raised. Several authors have presented "vascular factors" in their tables of etiologic factors. None, however, have given a clear demonstration to support inclusion of such factors in the tables. The reports of Lynch and of Pagel and Woolf, together with the experimental work of Smyth, would indicate that vascular factors as such are not important in the initiation of acute hemorrhagic pancreatitis. All the lesions of the pancreas alluded to in the literature as being caused by vascular changes were

focal in nature. In a recent study of the lesions of the pancreas in 100 cases of malignant hypertension not a single instance of diffuse hemorrhagic pancreatitis or diffuse pancreatic necrosis was encountered by Hranilovich and Baggenstoss. All the lesions were focal, and the majority were microscopic.

Although vascular factors may not be significant in the initiation of diffuse pancreatitis in man, they nevertheless may be of great importance in the progression and ultimate outcome of the disease process. Thus, whether obstruction of the pancreatic duct in man results in a relatively benign form of acute edematous or interstitial pancreatitis or whether it terminates in diffuse pancreatic necrosis may depend on vascular factors. The results of these experiments lend support to this viewpoint.

We were unable to demonstrate definitely that stimulation of secretion of pancreatic juice in rats exaggerates the changes in the pancreas after obstruction of the pancreatic ducts. Certainly, significant pancreatic necrosis did not occur under these conditions. This is in agreement with the reports of Popper and associates (9, 11). Popper and Necheles do believe that after injury to the pancreas a secretory inhibition of the pancreas occurs which resists all stimuli. However, it is obvious that the pancreas must be secreting simultaneously in the presence of obstruction of the duct before dilatation of the duct and the changes due to the action of the constituents of the juice can occur.

It has been established that the enzymes of pancreatic juice may be activated in the pancreatic ducts without contact with the intestinal juices. However, activation apparently is more pronounced if the latter occurs. Evidently the fat necrosis and other changes as observed in this study appear when extravasation of the pancreatic enzymes into the edema fluid occurs after obstruction of the duct or as a result of rupture or disintegration of ducts.

It is difficult and perhaps hazardous to attempt to correlate the experimental results with clinical findings in man. Nevertheless, it may be significant that the dilatation of ducts and acini and the degenerative changes and atrophy of acinar cells which occur after obstruction of the pancreatic duct alone simulate the histologic changes observed in fibrocystic disease of the pancreas in children. Baggenstoss, Power, and Grindlay have recently attributed the latter entity to congenital atresia of the pancreatic ducts. Associated with these changes in the pancreas of the rat there are a tremendous interlobular edema and the presence of numerous mononuclear leucocytes and occasional polymorphonuclear leucocytes. This exudative reaction is not observed in fibrocystic disease but approaches that observed in so-called acute edematous pancreatitis or acute interstitial pancreatitis which frequently is encountered by surgeons during the course of operations on the biliary tract. The latter entity is much more common than was realized in years past. Then acute hemorrhagic pancreatitis was the only form recognized clinically, and the only form to which experimental efforts of reproduction were directed. With the availability of determination of serum amylase and lipase for diagnostic purposes, it has become evident that the acute edematous form of pancreatitis is the much more common form of the disease. The limitation of attention to only the hemorrhagic form tended to confuse early experimental studies, for it was thought that pancreatitis occurred only if this hemorrhagic form was produced. Thus, it is conceivable that acute edematous pancreatitis is due to obstruction of the pancreatic duct. When pancreatic necrosis or hemorrhagic pancreatitis occurs, however, ischemia may be the additional factor which is responsible for these changes. To produce extensive and spreading acute pancreatic necrosis, a large area of pancreas evidently must be separated from the arterial blood supply.

It is well known that with permanent occlusion of the pancreatic ducts, fibrosis of the pancreas occurs. It is conceivable, therefore, that repeated acute obstruction of the pancreatic duct may be a factor in the pathogenesis of the clinical entity, chronic relapsing pancreatitis.

If obstruction of the pancreatic duct is the important factor in the causation of pancreatitis, the question arises as to the nature

of the obstruction. Spasm of the ampullary region, stones in the common or pancreatic ducts, edema of the papilla or duodenal mucosa, stricture or cicatricial stenosis of the papilla, all have been considered in the past. It is also difficult to be certain of the cause of ischemia when it is present in acute pancreatitis, although edema and inflammation, thrombosis of vessels, action of enzymes on vessels, resulting in their occlusion, and vascular spasm, all may be important factors.

SUMMARY AND CONCLUSIONS

Factors concerned in the pathogenesis of acute pancreatitis have been evaluated experimentally in the rat.

After partial or complete obstruction of the flow of pancreatic juice, pancreatic changes consisting of edema, inflammation, degeneration and atrophy of acini, and intrapancreatic and extrapancreatic fat necrosis occurred. Significant pancreatic parenchymal necrosis did not occur. The changes appeared analogous to those seen in acute edematous or interstitial pancreatitis in man.

Occlusion of the common bile duct so as to permit the mixing of bile and pancreatic juices under physiologic pressures did not alter the changes produced as compared with those occurring after obstruction to the flow of pancreatic juice without admixture with bile.

The production of temporary or permanent ischemia in addition to obstruction of the pancreatic ducts resulted in pancreatic parenchymal necrosis varying in severity with the degree of arterial obstruction to the pancreas. The lesions so produced may be analogous to acute hemorrhagic pancreatitis in man.

Complete devascularization of large portions of the pancreas generally resulted in ischemic infarcts, but occasionally acute pancreatitis with pancreatic necrosis and with fat necrosis without dilatation of ducts and acini occurred. Thus, a focal form of acute pancreatitis can result from prolonged severe and extensive ischemia alone.

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CUTE VASCULAR TRAUMA IN KOREAN WAR CASUALTIES

An Analysis of 180 Cases

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ACUTE injuries of major arteries always constitute a threat to life and limb. During time of war these injuries assume even greater importance be- use of the epidemic increase in numbers of ch lesions. The Korean conflict provided e opportunity for the observations recorded this communication. This analysis, which abodies 79 injuries of major arteries, 30 of inor arteries, and 71 of major veins, com- ises the personal studies of one of three servers working independently in Korea as embers of the Surgical Research Team of the rmy Medical Service Graduate School, ashington, D. C. Findings of the other two servers have already been reported (4, 5). t the same time, a similar program was nder way by Navy medical officers in the larine hospitals in Korea (7).

The most complete review of acute vascular injuries is the DeBakey and Simeone analysis of 2,471 cases from World War II. They found that the incidence of amputations from injury to major vessels of the extremities was 49.6 per cent. Of 81 suture repairs of these lesions, the amputation rate was 35.8 per cent. In the initial phase of the Korean War, attempts at anastomosis of damaged arteries were not much more rewarding (3).

MAJOR ARTERY INJURIES

During a 6 month period in Korea, 79 consecutive injuries to major arteries in 76 unselected patients were treated by the author at the 8055th Mobile Army Surgical Hospital (later named the 43rd Surgical Hospital). The distribution of these injuries is presented in Table I.

The 79 vascular injuries encountered were broken down as follows: lacerated 42, severed 31, contused with spasm 2, and contused with thrombosis 4. Most patients had multiple injuries. Complicating these were severe compound, comminuted fractures present at the site of the arterial injury in 12 cases with less severe compound fractures present in 5 other cases (Fig. 1a and b). All but 10 wounds, or 12.7 per cent, were caused by fragmenting missiles.

Thirty of the patients arrived in shock of varying severity. Thirty-seven were admitted with a tourniquet in place which had been applied from 40 minutes to 14½ hours previously, the average time being 4 hours. The overall time from injury to surgery averaged 10 hours with extremes from 3.5 to 28.5 hours. Of this interval, evacuation time to the hospital averaged 5.8 hours and time from admission to surgery an additional 4.2 hours. Resuscitation was often a problem and though the patients were sometimes admitted soon after injury, the time lost during resuscitation sometimes militated against recovery of the limb. This is a reflection of the severity of injury and shock in these patients.

Concomitant nerve injury, not necessarily at the site of the vascular injury, was evident in 36 of the 79 vascular injuries. Of these, there were 20 major nerve injuries, 9 minor nerve injuries, and 7 instances of nerve involvement believed due to anoxia, tourniquet, or mild contusion. Because of the multiplicity of wounds, prolonged use of the tourniquet, and periods of anoxia, it was difficult to determine the cause of nerve injury in some cases when the actual damage was not visualized.

Methods. Major vascular injuries were given priority evacuation along with other priority cases. High priority is important for resuscitation and surgery since every minute may be vital in salvaging a limb.

From the Division of Surgery, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C.

TABLE I.—THE DISTRIBUTION OF THE MAJOR ARTERIAL INJURIES

	No. of cases
Common carotid	4
Axillary	3
Brachial	25
External iliac	1
Common femoral	3
Superficial femoral	22
Popliteal	21
Total	79

Preoperative oscillometric studies were done on limbs showing absence of a pulse, unless the limb was in traction or a tourniquet was in place. Twenty-two of the 32 patients admitted without tourniquet had no palpable pulse in the injured extremities. Oscillometric readings in these limbs were almost universally zero, with only 3 showing a quiver of the oscillometer needle. Immediately following arterial repair, some cases showed better oscillometric readings on the repaired side than on the normal side but the group as a whole averaged 0.67 unit less on the repaired side.

An anatomic surgical approach was used regardless of location of the wound. An adequate incision was always made and proximal control of the vessel secured first.

TABLE II.—RESULTING AMPUTATIONS, VESSELS INJURED, AND CAUSE

Vessel	Injury	Time of injury to repair, hours	Type of repair	Cause of amputation
Axillary	Severed	24	Anastomosis	Muscles had undergone irreversible changes prior to vascular repair. Good blood flow was present through dead muscle at amputation
C. femoral	Spasm	11	Release of spasm	
C. femoral	Laceration	14¼	Arterial graft	
Popliteal	Laceration	16½	Anastomosis	
Popliteal	Severed	13¾	Arterial graft	
Popliteal	Laceration	11	Anastomosis	Venostasis
Popliteal	Severed and lacerated	6½	Vein graft	Compressed by slipping compound comminuted fracture of femur
Popliteal	Severed	12	Anastomosis	Partial amputation of foot 3 months later probably due to thrombosis

All repairs were by suture with 5–0 braided arterial silk, continuous everting mattress technique, intima to intima placement.

Two Pott's ductus or coarctation clamps plus arterial tissue forceps, a fine needle holder, and 5–0 braided arterial silk were the only additional equipment found necessary for peripheral vascular surgery. Each hospital receiving such patients should be so equipped.

All wounds were adequately débrided but all collateral vessels were preserved where possible. Even after arterial reconstruction, it often took the damaged muscle some time to bleed, making it difficult to evaluate properly the viability of the muscle distal to sites of arterial injury.

The repaired vessels were covered for nourishment and to avoid secondary infection. Coverage should be loose but adequate, and without primary closure of the skin. If infection occurs, it will often result in thrombosis at the site of repair.

To be sure there was no undue tension on the suture line, repairs at joint sites were inspected at completion of surgery by fully extending the joint and visualizing the repair site. These limbs were then flexed 10 to 15 degrees for 2 weeks but restrained only with adhesive tape to allow flexion but to limit extension. Limited active motion to improve the circulation was encouraged as soon as possible after surgery. When active motion was not possible, passive motion was utilized.

Delayed closure of clean wounds was done on the fourth to sixth postoperative day when the patient work load permitted. If wounds remained clean and healing uneventful, joints were gradually, fully extended and the patient ambulated after 2 weeks.

When bed space permitted, these patients were observed at the surgical hospital for 8 to 10 days, then evacuated to Army hospitals in Japan where primary follow-up studies were initiated. Those eligible for evacuation to the United States were subsequently evaluated further by arteriography, oscillometry, and skin temperature studies at Walter Reed Army Hospital. Inasmuch as some of the casualties were Ethiopian, Korean, Colombian, and Commonwealth patients, long term follow-ups are possible only on Americans.

It is fully realized that long term follow-up udies will be necessary for a complete evalu- ion of acute arterial repairs. However, it pears at this time that a very high per- ntage of limbs with arterial damage can be lvaged if the patient can be evacuated to a spital and resuscitated before irreversible uscle changes take place.

Results. Six patients with 7 arterial repairs opliteal 4, superficial femoral 2, common moral 1) died shortly after operation from uses other than arterial injury. For this ason adequate evaluation was not possible d these cases are eliminated from the analy- , except to mention any complication oc- rring before death. Summaries of these are ven in the addendum. Of the 72 remaining tients who survived, 8 subsequently came amputation of the involved limb. Thus, .1 per cent of the limbs were lost and 88.9 r cent were salvaged.

The reasons for which the 8 amputations re performed warrant some explanation. ve of these were performed within the first stoperative week and 3 subsequently. ven were in lower extremities and 1 in an pper extremity. Five amputations resulted om irreversible muscle changes which prob- bly had taken place prior to vascular repair. These muscle changes were obvious at the ime of reparative surgery in 3 cases, and the viability of the muscles was questionable in the 2 others. Muscle biopsies at the time of repair confirmed the gross observations. Cold injury was a complication in 2 of the am- putees. In these 5 cases, the time from injury to repair varied between 11 and 24 hours, with a mean of 16 hours. Restoration of blood flow was effected in the hope of salvaging the limb, or, at least, providing the longest possible viable stump. At the time of amputation there was a brisk flow of blood in the already de- vitalized muscles. If these 5 cases with irre- versible muscle damage at the time of repair are excluded, the amputation rate following repair in this series is 4.2 per cent and the limb salvage rate is 95.8 per cent.

A sixth patient came to amputation because of venostasis, with ensuing liquefaction of the muscles. The seventh amputation resulted from slippage of the fractured femur with com-

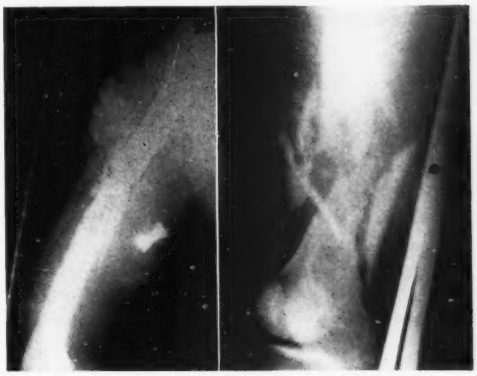

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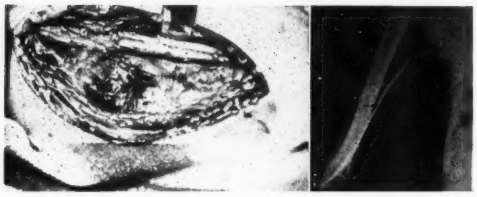
Fig. 1. a and b, Successful vascular repairs were done in the presence of compound comminuted fractures.

pression and thrombosis of the repaired ar- tery. The eighth patient required a transmeta- tarsal amputation 3 months later for dry gangrene of the toes; probably the result of a small embolus from the repair site and not directly due to initial failure of the repair.

Of the repairs in limbs subsequently am- putated (Table II), grafts were employed in 37 per cent of the cases, as compared to 19 per cent for the whole series. This is a further in- dication of the extent of the trauma which presented in these patients. It should also be noted that the injuries were to arteries at critical levels which may be expected to result in gangrene in a high percentage of cases if ligated.

FACTORS INFLUENCING LIMB SURVIVAL FOLLOWING BLOOD VESSEL SURGERY

Time lag. It is not possible to establish a specific time interval after which repair is no longer practicable because of muscle necrosis. There are many variables which make it impossible to determine clinically when mus- cle changes are irreversible. Factors to be considered are the length of time after injury, severity of the wound, the artery injured, the level of the injury, the number of collaterals damaged, the outside temperature, exposure, the state of shock, and anatomic variations. A decrease in the surrounding temperature (short of causing frostbite) appears to be advantageous. The converse also seems to be



a b

Fig. 2. a and b, A brachial artery anastomosis and arteriogram showing the repair site several months later.

true. During very hot weather, muscle changes and gangrene have been observed to occur much more rapidly.

Acute vascular injuries should be repaired in borderline cases of irreversible muscle damage even though the limb is expected to be lost. Restoration of blood flow may preserve some length of the limb or even a joint before a line of demarcation appears.

Tourniquets. The application of a tight pressure dressing was not always adequate for control of hemorrhage as evidenced by 47 per cent of these patients admitted with a tourniquet in place. Without control of the hemorrhage, resuscitation cannot be accomplished. Prolonged use of the tourniquet for resuscitation may result in a nonviable extremity, so a vicious cycle is created. In such cases, the bleeding artery was exposed and a clamp applied to the very end of it to preserve all of the artery possible for repair. A pressure dressing was then usually adequate, and resuscitation could be continued.

Many physicians are still not tourniquet-conscious. Tight Esmarch tourniquets have been found covered by external dressings. It is believed that a tourniquet should be applied in the field and left in place until removed by a medical officer with blood available to resuscitate the patient. A pressure dressing should then be applied tight enough to control the hemorrhage, as it will do in most cases. If watched carefully, the pressure dressing often can be loosened after a matter of 20 to 30 minutes but continued observation is necessary to prevent recurrence of hemorrhage as blood pressure rises.

Muscle changes. Many patients were admitted with muscles hardened by ischemia with contractures and fixed, frozen joints. These extremities were cold, spastic, anesthetic, and paralytic. After restoration of blood supply, the muscles swelled and fasciotomies were performed. At fasciotomy, the muscle was often found to be pale, swollen, and ischemic, and a blood-tinged transudate often ran out as the muscle bulged from the compartment. It was observed that muscles of the anterior tibial compartment of the leg and the flexor compartment of the forearm were the most vulnerable to swelling and broke down more quickly than others if fasciotomy was not done early. As more experience was gained, fasciotomy was done prophylactically in borderline cases.

After restoration of blood supply and the initial swelling, such extremities became warm; the swollen muscles softened, relaxed, and sensory and motor function gradually returned. This process sometimes took 2 to 3 days. In the lower extremities, peroneal nerve function was invariably slow to return.

Serial muscle biopsies were taken in many cases showing various stages of degeneration, fragmentation, hyalinization, and regeneration of muscle. In other instances, microscopically normal muscle was seen after prolonged periods of anoxia. This project was undertaken to study the condition of muscle and its blood supply at the time of surgery and to observe the progression of muscle degeneration and regeneration. It was hoped that the cause of irreversible muscle damage might be delineated as being due to muscle fiber death or secondary to venous, capillary, and arterial thrombosis.

In some of these cases, changes developed varying from microscopic areas of focal necrosis to loss of whole muscle compartments. Some of these muscles underwent complete sterile liquefaction. On dissection of these extremities after amputation, many small veins were found thrombosed while the arterioles were patent. One of these patients came to amputation 18 days after repair because of slow muscle changes. One compartment after another was débrided until only skin, bone, nerve, and vessels remained.

It is possible in some cases that restoration of the blood flow hastened muscle degeneration. Experimental work has shown that

rapid revascularization of ischemic muscle hastens degeneration. It has been suggested that there may be some similarity to frostbite where a slow, rather than rapid, return of blood flow and warmth may be important to survival of damaged muscle.

In the lower extremity, when muscle degeneration had taken place before restoration of blood supply, it was invariably found at amputation that the soleus muscle had undergone more extensive degeneration than the gastrocnemius.

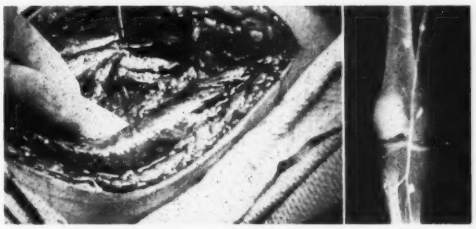
These muscle studies are still in progress and will be reported separately and in detail at a later date.

Types of repair. While simple suture repairs of lacerated arteries were held to a minimum in this series, some were done by others in the Theater. A high incidence of late thromboses has resulted following this type of repair. Except for the small, clean, knife-like laceration, it is difficult to evaluate, debride, and suture the damaged artery without constriction of the lumen. It is usually better to excise the damaged portion and do an end-to-end anastomosis.

It was possible to do a direct anastomosis in 65 per cent of the cases (Table III). The portion of artery excised averaged ¾ inch. With dissection of the artery for approximately 2 inches in each direction, an anastomosis could usually be done without undue tension (Figs. 2a and b, and 3a and b). Major branches and collaterals were preserved, although minor branches were at times sacrificed to gain arterial length.

Excised sections of damaged arteries were studied histologically for adequacy of débridement. Several sections taken from the cut ends of the artery adjacent to the anastomosis have shown microscopic changes including polymorphonuclear infiltration and irregularities of the internal elastic membrane, which might be interpreted by some as being due to inadequate débridement. Follow-up studies have shown no correlation with postoperative thrombosis in these cases.

Some anastomosed segments removed from amputated limbs and at autopsy have shown microscopic areas of infarction at the suture line. It has not been determined whether these changes represent inadequate débridement or changes secondary to the stripping of adventitia and vasa vasorum incident to suture of the vessel. It is possible that such infarctions may occur in many cases and that the infarcted area is replaced in the same manner as a graft. Details of histologic studies of arteries will be reported in a separate communication.



a b

Fig. 3. a and b, A popliteal artery anastomosis and arteriogram showing the repair site several months later.

Grafts were required in 19 per cent of the cases (Table III). Arterial defects up to 4½ inches in length were encountered, but, as already mentioned, the defects averaged ¾ of an inch. Both autogenous vein grafts and homologous arterial bank grafts were utilized. Autogenous vein grafts from ¾ inch to 3¾ inches and homologous artery grafts from 1 inch to 4¼ inches were used (Fig. 4a and b). The saphenous vein was most often used as a graft; however, the cephalic, basilic, and others were also used. The saphenous vein is usually of adequate size for most peripheral vessels and appears to be stronger than veins of upper extremities. Vein grafts are always turned end for end, when inserted, so the valves do not obstruct blood flow. Grafts

TABLE III.—THE FREQUENCY AND TYPES OF REPAIR UTILIZED

	No. of cases
Primary anastomosis	51
Autogenous vein graft	11
Homologous arterial graft	4
Suture repair	3
Removal of thrombus	1
Release of spasm	2
Conservative treatment	4
Ligation	3
Total	79

a b

Fig. 4. a and b, A massive avulsing wound of the upper arm prior to surgery and after débridement and insertion of a 3 inch saphenous vein graft into the brachial artery.

usually are not taken from the involved limb, especially if other major veins of the limb are damaged. Sometimes the companion vein of the artery may be utilized, if already damaged, but usually it is too large. Vein grafts should be chosen slightly smaller than the artery into which they are to be inserted to prevent overdilatation.

Homologous arterial bank grafts were preserved in a modified Tyrode's nutrient graft solution, up to 30 days. Availability of bank grafts saves time and is advantageous in cases in which, because of the patient's position at surgery, an autogenous vein graft is not always readily accessible.

Autogenous vein grafts have been more satisfactory than homologous arterial grafts. This has borne out our previous experience (1). Although no limbs were lost as a result of it, 2 of the 4 homologous arterial grafts in this group thrombosed within 4 to 8 weeks. The other 2, utilized in extremities which came to amputation, were patent at the time of amputation 6 days after insertion.

Ligation was reserved for noncritical arteries in which it was deemed unwise to do a repair and for patients who would not tolerate prolonged surgery. Of the 3 major arteries ligated in this series, the terminal brachial, involving ulnar and radial bifurcation, and the terminal popliteal, below the origin of the anterior tibial artery, were involved. Two of these patients were in such poor condition that they would not tolerate further surgery. In each case it was determined at surgery that the limb had adequate circulation for viability. Ligation of the concomitant vein at the time of artery ligation was not practiced and it is believed that it may even be a harmful procedure.

Previously, a very high percentage of injuries of the carotid arteries, ligated or repaired immediately, resulted in death or hemiplegia. It has been found in partially severed major arteries of extremities that if ligation is delayed several hours or days a much lower incidence of gangrene occurs. Such arteries may be ligated weeks later and gangrene is unusual. On this basis, it was decided that when the hematoma was self-contained and the hemorrhage controlled, all carotid injuries would be treated conservatively, particularly if an arteriovenous fistula was present. The wounds were débrided superficially and great care was taken not to dislodge the clot and to avoid wound infection. It was believed that even if the patient bled 1 or 2 days later, his chances of survival were much better after delayed, rather than immediate, surgery. We have had no occasion to regret this decision. Of the 4 cases treated conservatively in this group, 3 have since had successful definitive surgery and the fourth had apparently spontaneous closure of the arterial defect.

The same conservative treatment was applied to self-contained high subclavian injuries because of the difficult surgical approach, long operation, and dangers of massive hemorrhage and infection. Such lesions were

allowed to develop an arteriovenous fistula or false aneurysm and then were operated on subsequently.

While follow-up studies sometimes show some constriction at the suture line, actual thrombosis has been quite rare. These studies have also shown the repaired limb to average 1.6 oscillometric units less than the normal side. Several factors may influence these oscillometric changes—such as the multiplicity of wounds, nerve injury, scar tissue, or any constriction present at the repair site. These same changes may also alter skin temperature changes which on follow-up studies have averaged 1 degree less in the limb with the repaired vessel.

Complications. Postoperative complications of infection and hemorrhage must be watched for carefully. Infection may result in thrombosis or dehiscence of the arterial suture line with hemorrhage. Penicillin and streptomycin were used prophylactically in these cases and infection usually was not a problem. In fact, only 1 severe infection occurred—this about a vein graft—resulting in thrombosis of the graft. Dehiscence and hemorrhage may also occur from a poor anastomosis, inadequate arterial débridement, inadequate arterial coverage, or too much tension.

Hemorrhage from the suture line in the immediate postoperative period was not observed. It was reported in 3 cases in follow-up studies. One such patient, who was anuric and who was dialyzed, had repeated convulsions and bled from his suture line 12 days postoperatively into a nonhealing wound. This patient died. A second patient bled from his wound 21 days after operation, following delayed skin closure. The peripheral pulses were unaltered. After a second hemorrhage, 36 days postanastomosis, the pulses gradually disappeared. There was no surgical intervention or proof of the site of the hemorrhage, but this patient had a severe compound, comminuted fracture of the femur and had been in traction during this period. The artery may easily have been lacerated by a bone fragment. This patient is still in traction for the ninth month. A third patient bled from his suture line 14 days postoperatively. The vessel was ligated without limb loss. Two other patients had hemorrhage as a complication but not from the suture line. One of these, the third fatality listed in this series, had a compound comminuted fracture of the femur which lacerated the artery above the repair site. The other case of hemorrhage occurred 11 days postinjury with hemorrhage from the artery 1 inch above the anastomosis, presumably from a damaged area in the artery, overlooked at the time of surgery, and which later necrosed.

Thrombosis was not a problem in arterial repair. Anticoagulants were not used and are not considered necessary.

Although amputation resulted from arterial spasm alone in 1 case (Table II), this was rarely a problem. Spasm was treated variously at the time of surgery with 2½ per cent papaverine hydrochloride, warm saline packs, segmental periarterial sympathectomy, and 25 to 50 milligrams of intra-arterial priscoline. Postoperatively, repeated sympathetic blocks with 1 per cent procaine were used as indicated. Sympathectomy was not done in repair of these acute injuries. A second patient, treated for severe segmental spasm only, still has a patent artery but a slight constriction throughout the length of the site of the original spasm. Whether this was due to changes in the arterial wall, a thrombus within the artery, or to scar tissue and callus formation from the associated compound fracture, is not known.

The trauma causing the arterial damage, the vasoconstriction of the collaterals, plus shock and its accompanying peripheral vasoconstriction all combine to decrease the blood flow to a limb with arterial injury. As a result of this chain of events, some patients having major arterial damage even for a short period of time may exhibit muscle changes resulting from anoxia.

Compound comminuted fractures did not cause as high a percentage of complications as expected. While severe compound, comminuted fractures occurred in only 15 per cent of the arterial injuries, direct complications could only be attributed to the fractures in 2 cases previously mentioned. In one, the fracture slipped, compressing the repaired artery and requiring amputation. In

the other, laceration of the repaired artery was produced by the bone fragments requiring ligation of the artery.

Such fractures complicate vascular repairs by slipping and compressing or lacerating the vessel. Tissue pulled between the artery and bone is protective. To avoid damage to the repaired artery, pin fixation in a cast may be necessary in cases such as fractures of the distal femur. Fixation in casts should be reserved for those with concomitant fractures. Such casts should be bivalved immediately and taped together to allow immediate access to the repair site in the event of hemorrhage.

MINOR ARTERY INJURY

Thirty injuries to minor arteries were studied in other patients. Minor arteries injured included the profunda brachii, profunda femoral, radial, ulnar, and anterior and posterior tibial. When only one of two minor arteries to an extremity was involved (such as an injured radial but intact ulnar), the injured vessel was ligated. In no case did this procedure lead to complication. In instances in which both vessels were involved, the limb was invariably so macerated and shattered that amputation was necessary. In such cases one, or both, of the arteries would have been repaired had there been viability.

VEIN INJURIES

Concomitant major vein injuries were found in 50 cases with major arterial injuries. Other major vein injuries were added to this group to bring the total to 71. Fifty-eight of these veins were ligated. Complications ranged from none to various degrees of venostasis. In 1 patient, loss of an extremity resulted from severe venostasis. The popliteal, greater and lesser saphenous veins had been severed. While there was good arterial inflow, the muscles gradually liquefied and required amputation. On dissection of the leg the arteries were all patent but the veins were all thrombosed. This observation has also been recognized by other investigators and is similar to a massive venous thrombosis.

TABLE IV.—LOCATIONS OF MAJOR VEINS REPAIRED

	No. of cases
Popliteal	5
Common femoral	3
Vena cava	1
External iliac	2
Superficial femoral	2
Total	13

After complications were observed following venous ligation, major vein injuries, especially at critical levels, were carefully evaluated for repair. An evaluation of an extremity should be done at the time of surgery to determine the extent of other vein injuries before a repair is done. While the author has done numerous venous repairs at elective surgery (6), it was realized there was more danger of thrombosis and embolism in acute trauma. However, venous repair is believed to be a safe procedure if the clots are carefully removed and the vein is properly débrided and sutured. The size and number of wounds, size and level of vein injured, and the number of collateral veins injured are all factors that should be considered in determining whether or not a vein should be repaired.

Venous repairs were done by simple over-and-over suture except for 1 case in which anastomosis by a continuous everting type suture was carried out. Only 13 major veins were repaired in this group, 12 by lateral suture and 1 by end-to-end anastomosis (Table IV). No anticoagulants were used in these venous repairs.

Two patients early developed a thrombophlebitis of the superficial veins of the leg, but in each case the greater saphenous system had been previously ligated at the time of surgery. Follow-up studies have shown that when repair resulted in decrease in size of the lumen, a high percentage of the veins thrombosed. Thrombosis occurred after the initial 8 to 10 day period of observation. Venostasis has not been a major problem at follow-up. It is difficult to place the cause of persistent swelling in some cases because many have neurologic, venous, lymphatic, and multiple muscular injuries.

SUMMARY

1. One hundred eighty cases of acute vascular injuries were studied in Korean War wounded. These consisted of 79 major artery injuries, 30 minor artery injuries, and 71 major vein injuries.

2. After repairs of the major arterial injuries, 88.9 per cent of the limbs were salvaged and 11.1 per cent amputated.

3. The amputations included 5 limbs which had undergone irreversible muscle changes prior to vascular repair. The other 3 amputations resulted from complications of repairs.

4. Fasciotomies were found to be valuable adjuncts after arterial repair in limbs with borderline muscle changes.

5. A specific time interval after which arterial repair could not be done was not established.

6. Tourniquets should be applied and left in place until they can be removed by a doctor with adequate blood for resuscitation.

7. All degrees of muscle degeneration to regeneration were observed in cases of delayed arterial repair.

8. The major methods of arterial repair were end-to-end anastomosis and use of autogenous vein grafts and homologous artery bank grafts. Autogenous vein grafts in arteries have been far more satisfactory than homologous artery grafts.

9. Complications, including postoperative hemorrhage, infection, spasm, and thrombosis, were rare. Antibiotics were used. No anticoagulants were administered.

10. Thirty minor arteries were ligated without complications.

11. Seventy-one injuries to major veins were treated with some complications which led to the successful repair of 13 major veins.

12. Immediate repair of injuries to major arteries is practical. All major arteries should be repaired except when the additional time required for surgery endangers the patient's life. While some limbs survive major artery ligation, they are not functionally equal to the limb with a successful vascular repair. If thrombosis should occur at the repair site, the process will often be slow enough to allow collateral function to preserve the limb. If patients with vascular injuries can be brought to surgery before irreversible muscle changes take place, a very high percentage of limbs can be salvaged.

ADDENDUM

1. The first death occurred in a patient admitted in deep shock with a common femoral artery injury. Cardiac arrest occurred soon after anesthetic induction. He was resuscitated by cardiac massage, and while his chest was being closed an artery graft was inserted into the femoral artery defect. He died 4 hours later.

2. A second patient had a severed popliteal artery plus injuries to all extremities, abdomen, and chest. He was in deep shock for many hours. The artery was anastomosed while abdominal surgery was being done. Postoperatively, the patient lived only 38 hours.

3. A third patient with superficial femoral artery injury and multiple other injuries was admitted in profound shock. His condition was so poor that, after anastomosis of the artery, other débridements were not completed. After surgery, he continued to be irrational and although placed in a spica cast, the compounded femur lacerated the artery above the repair site on the third postoperative day. Since his condition did not permit prolonged surgery, the artery was ligated. The leg was amputated 9 days later. The patient died of cerebral damage a few days after evacuation.

4. The fourth patient was admitted in profound shock with a severed superficial femoral artery and cerebral anoxic changes. After a quick, easy arterial repair, the patient continued to be mentally hazy and became anuric. He was evacuated to the artificial kidney center. He had repeated convulsions, and 12 days after surgery hemorrhaged from the arterial repair. The artery was ligated. Two days later the patient died of cardiac arrest during attempted further débridement.

5. A fifth death occurred in a patient with a popliteal artery injury. The arterial injury was easily and successfully repaired but the patient died following a subsequent negative abdominal exploration performed at another hospital.

6. The sixth death occurred in a patient admitted in profound shock with severe injuries to both popliteal arteries, buttocks, back, all extremities, and compound, comminuted fractures of the femur. One popliteal artery was anastomosed while a colostomy was being done. The other popliteal artery was ligated in its terminal portion below origin of the anterior tibial artery. The patient's condition did not permit completion of his débridement. On return to surgery at a later date the patient developed pulmonary edema and died.

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COLONIC BLEEDING AND DIVERTICULAR DISEASE OF THE COLON

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THE purpose of this paper is to describe 4 cases of massive colonic bleeding associated with diverticulitis and to report a study of the incidence of rectal bleeding in 347 cases in which the underlying etiology was diverticulosis or diverticulitis coli. Also reviewed are an additional 38 cases of diverticular disease with concomitant carcinoma of the large bowel. Although the commonest source of colonic bleeding is carcinoma, massive hemorrhage is more often associated with peptic ulcer, esophageal varices, or ulcerative colitis. Its occurrence with diverticulitis, and even diverticulosis, has been reported occasionally. Bleeding includes, here, all forms of blood loss per rectum, whether occult, melena, bright red, or massive.

Since the nineteenth century anatomists Virchow, Cruveilhier, and Rokitansky first described diverticula of the colon, many clinical and pathologic aspects of the condition have been recorded in the literature. Rectal bleeding as a complication, however, has not received much attention. In 1907, Mayo, Wilson, and Giffin (7, 8) first contributed to the surgical management of the disease with sigmoid resection in cases of chronic intestinal obstruction. Since then the surgery of diverticulitis and its complications has often been discussed, but again, the surgical management of associated bleeding has not been emphasized. Hartwell and Cecil in 1910 and Beer and other early twentieth century physicians described and amplified various phases of the condition and delineated the place of conservative therapy in its management. The first widespread use of contrast media to study colonic disease indicated that the relative incidence of diverticulosis was 5 to 10 per cent of all patients examined over 40 years of age. A further estimate was reported by Kocour in 1937 who found diverticula present in 5.2 per cent of 17,000 consecutive autopsies with 85 per cent located in the descending or sigmoid colon. If, as we wish to demonstrate, an appreciable percentage of such patients have rectal bleeding in some form, it adds a great deal to the significance of diverticulosis as a consideration in differential diagnosis, whether other complications have developed or not.

The pathogenesis of acquired diverticula has been assumed to be an outpocketing of mucosa through the muscular layers at the point of emergence of a nutrient artery to an appendix epiploica. There is no proof of this, and supposed etiologic factors such as constipation and degenerative processes are speculative. Bleeding from the diverticulum is said to be due to erosions of the accompanying vessel secondary to pressure, trauma, or infection, and is often associated with arteriosclerosis, and sometimes hypertension.

METHOD

This study is composed of a series of well documented cases of diverticulosis and diverticulitis admitted in a 10 year period, 1943 to 1953, to the Peter Bent Brigham Hospital. There are 385 cases in which a careful attempt was made to correlate clinical observations with the operative and pathologic findings available. Of these, 38 had carcinoma of the colon and rectum. Rectal bleeding, of any degree, was considered a complication of diverticulosis or diverticulitis only after more common causes had been ruled out by gastrointestinal series, barium enema, and sigmoidoscopy. Four additional cases of exsanguinating rectal bleeding which proved to be secondary to diverticulitis are reported in some detail. Two of these were cared for in Boston veterans' hospitals.[1]

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[1]Boston Veterans Administration Hospital and West Roxbury Veterans Administration Hospital.

TABLE I.—COMPLICATIONS OF DIVERTICULITIS REVIEWED IN 111 CASES WITHOUT CARCINOMA AT THE PETER BENT BRIGHAM HOSPITAL 1943 TO 1953

	No. of cases
Bleeding	42
Perforation	9
Abscess	36
Intestinal obstruction (usually colonic)	44*
Fistula formation	
Abdominal wall	4
Rectovaginal	6
Enterovesical	1
Abscess+obstruction	7
Abscess+fistula+obstruction	3
Total complications	151

*11 with associated bleeding.

RESULTS

The cases are divided into diverticulosis and diverticulitis. The types of rectal bleeding considered are: (1) occult bleeding demonstrated by test, usually guaiac[1]; (2) serious blood loss, in which there is a history of bright red rectal bleeding, or tarry stools, and a low hematocrit may be demonstrated; (3) massive bleeding in which shock develops and transfusions are necessary.

Of 111 patients with diverticulitis without associated carcinoma, admitted to the Peter Bent Brigham Hospital, 42, or 37 per cent exhibited rectal bleeding. Study of these patients revealed that 31 who had clinical and roentgen evidence of sigmoid diverticulitis produced 2 or more stools positive for occult blood during their hospital stay. None of this group had gross evidence of rectal bleeding, and there was no laboratory evidence of anemia. Nine patients gave a history of rectal bleeding on admission and had either gross blood in the rectal ampulla or stools which were strongly positive to guaiac test. Two cases presented the problem of uncontrolled rectal hemorrhage, and despite blood replacement and conservative management, required surgical exploration as a lifesaving measure.

Other authors have recorded the incidence of rectal bleeding in diverticulitis as follows: Young and Young reported 26 per cent, Morton 20 per cent, Mayo (6) 8 per cent, Swinton 15 to 20 per cent, and Rankin 17 per cent. It may be that the higher incidence in this series is the result of the more frequent use of tests for occult blood in the feces in the routine work-up of hospital admissions in recent years.

Also, the incidence of rectal bleeding associated with 236 cases of diverticulosis without carcinoma was noted. The detection of rectal bleeding in 39 or 16 per cent of these cases is important because such a high incidence has not been reported previously, although reports such as those of Stone have appeared in the literature, indicating that bleeding does occur. Of the 39 patients presenting evidence of rectal bleeding, 18 passed bright red blood per rectum prior to admission to the hospital. Twenty-one patients, with diverticulosis by barium enema, passed guaiac positive stools with no clinical or roentgenologic evidence of any other bleeding site.

In the Peter Bent Brigham Hospital series a study was made of the complications associated with diverticulitis.[2] Table I shows the variety of cases of perforation, abscess formation, intestinal obstruction, and fistulas. There were 42 cases with rectal bleeding, 11 had associated intestinal obstruction, and 1 had abscess formation. The remaining 30 had no other major complication of diverticulitis. It is important to note that about one-third of the patients with colonic obstruction had bleeding, further complicating the differential diagnosis of carcinoma. We believe that rectal bleeding, per se, associated with diverticulitis, has no significant relationship to the other major complications, except that of obstruction.

Table II shows the percentage of patients with diverticulosis or diverticulitis who had an associated carcinoma of the colon or rectum. These percentages do not indicate any relationship between the two diseases and are in the same range reported by others. Actually, of 385 cases indexed as "diverticulitis" and "diverticulosis" reviewed, in only 14 or 3.6 per cent was a carcinoma of the colon present in an area of diverticula, where the two com-

[1]The benzidine dihydrochloride test, as described by Mendeloff, is to be preferred as a screening procedure for detecting occult blood in feces. The reagents are benzidine dihydrochloride and barium peroxide.

[2]These complications, not including bleeding, were often multiple, and occurred in 62 of the 111 patients.

plicated each other and made differential diagnosis difficult. The x-ray diagnosis of diverticulosis is often not listed at the time of the patient's discharge if he also has cancer; consequently, such a simple statistical analysis is misleading. In order to determine the absolute incidence of associated carcinoma, 466 cases of patients with carcinoma of the colon and rectum admitted between 1943 and 1953 were reviewed and 38 (8 per cent) with a concomitant x-ray diagnosis of diverticulosis found. Thus, the incidence of diverticulosis in this group was only 8 per cent which is roughly the expected figure in the population as a whole who are in the middle-age group and beyond.

There are only isolated reports dealing with the massive hemorrhage that may occur in diverticular disease of the colon. This is a rare occurrence. Four cases are reported herewith. It is sufficiently dramatic, however, to stimulate more attention than it has been given in the literature. Morton, Stone, Turnbull, and Smith have described shock-producing, but self-limited, colonic hemorrhage in patients with no other source of bleeding demonstrable. In Turnbull's review of 151 cases of diverticular disease there were 9 patients (6 per cent) admitted with massive rectal hemorrhage who responded well to blood replacement and conservative management. Three of these patients had known hypertension, and 5 had generalized arteriosclerosis with accompanying arteriosclerotic heart disease. Three deaths occurred subsequently, all on the basis of marked cardiovascular disease, exacerbated by the initial hemorrhage and resulting shock. Swinton noted 2 cases of patients who were subjected to primary sigmoid resection because of repeated hemorrhages accompanying diverticulitis. Thompson reported 2 cases of exsanguinating bleeding from diverticulosis alone. Recently, a single case of massive hemorrhage was reported by Cate in a patient with diverticulosis involving the entire large bowel. An emergency subtotal colectomy was performed with cessation of bleeding and eventual recovery of the patient.

The 4 cases of massive bleeding observed will now be reported in detail. Of these 4 patients, 3 succumbed.

TABLE II.—DIVERTICULAR DISEASE AND CARCINOMA

	Diverticulitis No. cases	Diverticulosis No. cases
Bleeding		
With carcinoma	4	23
Without carcinoma	42	39
No bleeding		
With carcinoma	2	9
Without carcinoma	69	197
Total cases	117	268
Per cent, carcinoma	5	11

CASE REPORTS

CASE 1. P.F.O., No. 39066, West Roxbury Veterans Administration Hospital. This patient was a 62 year old white salesman, admitted to the hospital on December 24, 1951 complaining of crampy lower abdominal pain and massive rectal bleeding of 4 hours' duration. The present illness revealed that 4 hours prior to admission the patient passed large amounts of dark blood per rectum on 5 separate occasions. Just prior to admission he passed 1 stool which contained a great deal of bright red blood. The patient denied any previous change in bowel habits, having had one formed brown stool per day for many years. There were no other gastrointestinal symptoms and no history of weight loss or fatigue. Of significance in the past history is the fact that the patient was a known hypertensive of 3 years' duration and was digitalized.

Physical examination. A well developed, obese white male with cool, pale, moist skin was seen. The temperature was 100, pulse 100, blood pressure 130/100. The lung fields were clear to percussion and auscultation. Examination of the heart showed a regular sinus rhythm and definite cardiomegaly. The abdomen was soft and nontender to deep palpation. A firm, smooth liver edge was palpable 2 fingerbreadths below the right costal margin. There were no distended veins over the anterior abdominal wall, and no evidence of ascites was present. Peristalsis was active. Rectal examination revealed large quantities of dark red blood and clots.

Laboratory data. The hematocrit was 27 per cent, the white blood cell count 14,500 with 85 per cent polymorphonuclear leucocytes. The urinalysis was negative; the nonprotein nitrogen, fasting blood sugar, serum sodium, chloride, potassium, and carbon dioxide combining power were normal. Total plasma protein was 5.7 grams, with a normal albumin-globulin ratio.

Hospital course. Anteroposterior and lateral views of the chest revealed left ventricular hypertrophy with no evidence of congestive failure. An upper gastrointestinal series was entirely normal. A barium enema demonstrated extensive diverticulosis and diverticulitis of the descending and sigmoid colon. No other large bowel abnormalities were visualized.

Sigmoidoscopy to 20 centimeters showed the bowel to be normal except for the presence of large clots of dark blood. Aspiration of the gastric contents showed no evidence of gross blood, and the material was guaiac negative. The patient received 3,000 cubic centimeters of whole blood during the first 8 hours of his hospitalization with an increase in hematocrit at the end of this time only to 29 per cent. In the first 12 hours of his hospital stay he had received 4,500 cubic centimeters of whole blood and still was bleeding massively by rectum. The blood pressure during this period ranged between 120/80 and 150/100 millimeters of mercury. A tachycardia was present, and the patient was slightly febrile. Eighteen hours after admission the patient was operated upon. The only positive finding consisted of an area of diverticulitis in the midsigmoid region with induration, thickening, and redness of the bowel wall and mesentery. Because of the patient's critical condition during the procedure, it was elected to do a Mikulicz resection of this area of diverticulitis. Postoperatively, he received an additional 1,500 cubic centimeters of whole blood and maintained a systolic blood pressure between 150 and 200 millimeters of mercury.

Following the Mikulicz resection all evidence of rectal bleeding ceased. Although the bleeding point had apparently been resected, the patient's cardiovascular system progressively deteriorated. Auricular flutter was evident by repeated electrocardiograms and did not respond to rapid digitalization. Twenty-four hours following operation, with no further evidence of hemorrhage, the patient expired. Postmortem examination was carried out and confirmed the final clinical impression of congestive failure on the basis of hypertensive cardiovascular disease. A thorough examination of both the upper and lower gastrointestinal tract did not reveal any source of the rectal bleeding. Pathologic examination of the resected 10 centimeters of sigmoid colon demonstrated evidence of diverticulitis. Four out of 5 sectioned diverticula showed areas of engorged granulation tissue replacing a part of the mucosa. In addition, the lining of one of these was superficially ulcerated, with hemorrhage into the granulation tissue.

A Mikulicz resection appeared to be the safest way to remove this man's presumed source of bleeding. He did not survive long enough to prove that his bleeding points had been removed, though no other source of hemorrhage was found at postmortem examination. His death may have been the result of overtransfusion. A part of his early deterioration may have been on the basis of cardiac failure as well as hemorrhage, a situation in which the proper balance of blood replacement with loss and proper timing of operation may be extremely difficult to achieve.

CASE 2. N.M.B., No. U185, Boston Veterans Administration Hospital. This 69 year old white construction engineer was admitted to the hospital complaining of crampy lower abdominal pain and rectal bleeding of approximately 4 days' duration. The patient apparently had been well until the onset of the pain and generalized malaise 4 days prior to admission. On that day, he noted rectal bleeding, passing bright red blood and dark clots on 20 different occasions. Frequent semiformed stools containing small amounts of blood were passed daily, and 12 hours prior to admission the patient passed a large grossly bloody stool and became faint and dizzy. He was then hospitalized. Of significance in the past history was an episode of melena 3 years prior to admission which occurred suddenly without any accompanying gastrointestinal complaints. The patient was studied for 48 hours at that time and received a blood transfusion. The hemorrhage ceased spontaneously with no bleeding site determined. The patient's general health had been satisfactory. The review of systems did not reveal any bleeding tendencies and there was no history of hypertension or cardiovascular disease.

Physical examination. The temperature was 102.8, pulse 112, respirations 24, blood pressure 90/56. The patient was a well developed, asthenic, white male with warm, pale, moist skin. Examination of the abdomen revealed slight generalized distention and tenderness to deep palpation in both lower quadrants. No masses were palpable. Peristalsis was hyperactive. Rectal examination demonstrated the presence of large amounts of dark blood clots with some bright red blood. There was no evidence of a rectal mass.

Laboratory data. The hematocrit was 20 per cent, white blood cell count 24,000 with 80 per cent polymorphonuclear leucocytes. The urinalysis was negative. Nonprotein nitrogen and fasting blood sugar were within normal limits. The prothrombin was normal.

Hospital course. A barium enema showed an area of spasm in the sigmoid colon and numerous scattered diverticula. A perforation of the descending colon was noted just above the 10 centimeters area of spasm, with a small amount of barium passing out into a pericolic abscess. An upper gastrointestinal series was negative. Sigmoidoscopy to 25 centimeters was negative except for the presence of bright red blood. Immediately following admission, intravenous fluids and whole blood were started with improvement in the patient's general condition and an increase in blood pressure to 110/90 millimeters of mercury. Approximately 5 hours after admission, the patient was taken to the operating room where laparotomy through a left rectus incision revealed an area of diverticulitis in the sigmoid colon adherent to the parietal peritoneum. A small amount of cloudy fluid was present in the peritoneal cavity as well as a loculated collection of barium. After this brief exploration, a right transverse colostomy was carried out. Postoperatively, the patient developed ileus,

which was partially controlled with Miller-Abbott tube suction. No further rectal bleeding was encountered, but by the third postoperative day a diffuse bronchopneumonia had developed, accompanied by spiking temperatures ranging between 102 and 105 degrees. The patient became progressively dyspneic and required frequent endotracheal aspirations. On the evening of the third postoperative day he expired. No postmortem examination was allowed. The final clinical impression was bronchopneumonia and bilateral lower lobe atelectasis, peritonitis, and diverticulitis.

On clinical grounds this appears to be another example of massive bleeding from acute diverticulitis. Because of the associated sigmoid perforation, a diverting colostomy was the procedure of choice. However, insufficient time elapsed prior to demise to determine whether the bleeding was controlled.

CASE 3. A.D.C., No. 6F714, Peter Bent Brigham Hospital. This patient was a 63 year old white, congenitally paraplegic male, who was admitted to the hospital complaining of massive rectal bleeding of 18 hours' duration. The present illness began 2 years prior to admission when he first noted small amounts of bright red blood coating his bowel movements. He was examined at a neighboring hospital, where a hemorrhoidectomy was performed. All rectal bleeding ceased following this procedure until 9 months prior to admission, when the patient again noted the presence of bright red blood in small amounts coating his stools. There were no associated gastrointestinal symptoms at this time. Seven months prior to admission he visited another hospital where sigmoidoscopy was negative but a barium enema revealed diverticulosis of the sigmoid colon. During the last 6 months the patient had noted the onset of intermittent, mild, right lower quadrant pain, radiating to the left lumbar area. In this same interval increasing constipation was noted, with stools occurring once every 2 days, with the liberal use of mild cathartics. No further rectal bleeding or melena was observed until 18 hours prior to admission when he passed a large, black, liquid stool. Following the initial melena, 10 to 12 small tarry stools were noted. An increasing amount of bright red blood was observed, mixed with the tarry material, during the 3 hours immediately prior to admission. A steady aching right lower quadrant pain accompanied the rectal bleeding and was associated with occasional left lower quadrant crampy abdominal pain. Past medical history revealed several operations on the patient's lower extremities to correct marked flexion contractures of hips. Review of systems indicated that he had been hypertensive for at least 2 to 3 years. There was no evidence of congestive heart failure.

Physical examination. The temperature was 98, pulse 120, respirations 20, blood pressure 135/90. The patient was a well developed, moderately obese, partially paralyzed white male in no acute distress. The abdomen was slightly distended with moderate tenderness to deep palpation in the right lower quadrant. No masses were palpable, and peristalsis was normal to auscultation. Examination of the lower extremities revealed marked flexion contractures of the hips, accompanied by muscular atrophy. Rectal examination was negative, except for the presence of bright red blood and dark clots.

Laboratory data. The initial hematocrit was 38 per cent, white blood cell count 11,000 with 84 per cent polymorphonuclear leucocytes and normal platelets on smear. Urinalysis was negative. Blood urea nitrogen, fasting blood sugar, and prothrombin per cent were all within normal limits. The clotting time on admission was normal. An electrocardiogram showed left ventricular hypertrophy.

Hospital course. Sigmoidoscopy was essentially negative except for the presence of a large amount of blood and a 1 by 2 centimeter pedunculated polyp, 9 centimeters from the external sphincter. There was no evidence of bleeding from the polyp, but blood was seen coming down from above. A barium enema was performed 8 hours following admission and showed no abnormality except multiple diverticula of the sigmoid colon. The patient received 2,000 cubic centimeters of whole blood during the first hospital day, and his blood pressure remained constant at 140/80 millimeters of mercury. On the morning of the second hospital day, after a total of 3,000 cubic centimeters of whole blood, the patient's hematocrit had dropped to 23 per cent. Thirty-six hours following admission an upper gastrointestinal series was performed, which was entirely negative. On the evening of the second hospital day, after a total of 5,000 cubic centimeters of whole blood, the patient continued to bleed massively per rectum and, as a last resort, he was taken to the operating room, where a laparotomy was performed. A localized area of diverticulosis and diverticulitis involving the sigmoid colon was found. There was no other disease evident. It was elected to do a Mikulicz resection of this area with the hope that the bleeding would be controlled thereby. In the immediate postoperative period all rectal bleeding ceased and the hematocrit stabilized at 45 per cent. During this period, however, the patient developed a severe bronchial asthma which was accompanied by marked dyspnea and cyanosis. Twelve hours following operation, he aspirated gastric contents, after which his condition rapidly deteriorated. He expired, 3 days following admission, as a result of aspiration pneumonia without further evidence of rectal bleeding. An autopsy was performed, and an extensive examination of the gastrointestinal tract failed to reveal any other possible bleeding point. Examination of the resected specimen of sigmoid colon revealed extensive diverticulitis with edema and induration, as well as ulceration in several of the diverticula.

This patient had been in apparent good health prior to the onset of massive rectal

bleeding. Laparotomy was performed because all conservative methods failed to control the hemorrhage. Following a Mikulicz resection of his diverticulitis there was no further bleeding, with the blood pressure and hematocrit remaining stable. The fact that there was no rectal bleeding in his immediate postoperative course is not proof that his bleeding point had been resected. However, the lack of other sources at postmortem examination is quite conclusive. In retrospect, the chances of a favorable outcome would have been much enhanced had operation been performed earlier. It is possible that failure to appreciate the potentially dangerous nature of diverticular bleeding was in part responsible for the delay.

CASE 4. E.F., No. 7B66, Peter Bent Brigham Hospital. This 72 year old spinster was admitted to the hospital for the second time on August 13, 1953 complaining of severe rectal bleeding of 3 days' duration. The patient was well until 1 month prior to admission when moderate constipation was noted with hard brown stools produced only after catharsis. There was no accompanying abdominal pain, fever, or vomiting, and the patient denied the presence of blood in her stools then. The constipation continued until 3 days prior to admission, when bright red blood was first discovered in a formed stool. Following this episode, the patient passed large amounts of bright red blood and dark clots per rectum and noted progressive weakness and dyspnea.

Past history revealed that in June, 1950, this patient had been hospitalized for 12 days for treatment of diverticulitis. Severe left lower quadrant pain and fever were present for 3 days prior to admission but subsided rapidly with conservative therapy. There was no gross rectal bleeding associated with this episode, and repeated stool guaiacs were negative for occult blood. Barium studies of the colon revealed extensive diverticulosis of the sigmoid and descending colon and an area of spasm in the midsigmoid region. The patient was discharged on a low residue diet and followed carefully. Barium enemas were performed at 6 month intervals.

Systems review showed the presence of arteriosclerotic heart disease and a myocardial infarction which occurred in May, 1950. There had been no evidence of congestive failure, but the patient admitted to a moderate hypertension of 5 years' duration.

Physical examination. Her temperature was 100, pulse 100, blood pressure 140/86. The skin was pale, cool, and moist, with fair turgor. Palpation of the abdomen revealed no distention, tenderness, or rectus spasm. Rectal examination was negative except for the presence of dark clots and bright blood. Sigmoidoscopy to 15 centimeters did not reveal the site of bleeding.

Laboratory data. The hematocrit was 25 per cent, white blood cell count 8,200 with 73 per cent polymorphonuclear leucocytes. The blood urea nitrogen was 13 milligrams per cent and fasting blood sugar 98 milligrams per cent. The liver function studies were normal, including a normal prothrombin. Urinalysis on admission was negative.

Hospital course. Shortly following admission the patient received 1,500 cubic centimeters of whole blood, with a rise in hematocrit to 37 per cent. Her blood pressure stabilized at 170/100 millimeters of mercury and the rectal bleeding diminished in intensity. All stools during the first 4 hospital days contained small amounts of dark blood, but there was no further massive rectal hemorrhage. A barium enema again demonstrated diverticulosis and irritability but no real spasm at the sigmoid level. Upper gastrointestinal series was negative. On August 18, 1953, 5 days after admission, a decision was made to explore the lower abdomen while the patient's condition was still favorable. Laparotomy revealed a 22 centimeter segment of sigmoid colon adherent to the lateral peritoneal reflection with some pericolitis but no abscess formation. Sigmoid resection was performed with an associated cecostomy. Pathologic examination of the resected specimen demonstrated chronic diverticulitis but no definite bleeding point was discovered. Postoperatively, the course was complicated by a spiking temperature and a mild electrolyte imbalance. These responded to antibiotics and parenteral fluid therapy. No further rectal bleeding was encountered and the hematocrit and blood pressure remained constant. The cecostomy tube was removed and at discharge the patient was producing one formed, brown stool per day.

This was a case of recurrent diverticulitis resulting in massive rectal hemorrhage which was successfully controlled by sigmoid resection when the patient's condition was optimal. There was not the same degree of exsanguination noted in the previous case report and operation was performed earlier in the course. A short follow-up period of 5 months has revealed no further rectal bleeding.

DISCUSSION

These 4 cases are added to those few reported of massive rectal bleeding associated with diverticulitis. Although these are rare, the high mortality makes it mandatory to consider the diagnosis as a positive entity, and not fall back on the time-consuming "diagnosis by exclusion." If the upper gastrointestinal tract is clear, ulcerative colitis absent by proctoscopy, and diverticula present

by x-ray examination, early operation is essential.

There seemed to be a recurring pattern in the patients reported here with massive bleeding. They were all over 60 years of age. (In the Peter Bent Brigham Hospital series the average age of those patients with diverticulitis was 63 years, with diverticulosis 64 years. There were 50 males and 61 females in the group with diverticulitis, 105 males and 131 females in the group with diverticulosis.) Three of the 4 had a history compatible with hypertensive cardiovascular disease.

The incidence of hypertension in those patients with bleeding and without carcinoma in the entire series was noted to be 6 with diverticulitis and 8 with diverticulosis. This constitutes 17 per cent of the cases reviewed.

The conclusion may be drawn that, given an elderly, hypertensive patient with exsanguinating colonic hemorrhage, in the presence of diverticular disease, the decision to operate should be made early, after the initial blood replacement and chart stabilization have been achieved. A 12 hour period of observation should be sufficient in this situation. This would eliminate the predicament found in Case 3 in which surgery was resorted to as a last therapeutic measure. If one cannot determine the source of bleeding at laparotomy and sigmoid diverticulosis has been established, it may be wise to resect the sigmoid colon with the hope that this will eliminate the bleeding point. If the situation is not urgent and one is faced with recurrent bouts of hemorrhage, the treatment of choice may well be subtotal colectomy, removing the colon involved with diverticulosis. This is the more common situation. Such a patient responds well to blood transfusions and conservative management, rarely requiring emergency surgical intervention.

One must remain aware of the high incidence of colonic bleeding in diverticulitis and diverticulosis if he wishes to manage patients with lower gastrointestinal hemorrhage intelligently. It should be emphasized that the incidence of colonic bleeding and particularly of massive hemorrhage is great enough to warrant its positive inclusion in differential diagnosis.

Cancer of the colon remains, of course, the commonest cause of colonic bleeding, overt or occult; however. it is relatively uncommon as a cause of massive exsanguinating hemorrhage.

SUMMARY

The incidence of bleeding per rectum accompanying diverticulitis in a series of 111 cases without associated carcinoma of the colon was found to be 42, or 37 per cent. The incidence in a series of 236 cases of diverticulosis was 39, or 16 per cent. Four cases of massive colonic hemorrhage with diverticular disease as the principal etiologic factor are described in some detail. This experience seems to indicate that early operation is advisable in such a situation.

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SURGICAL STATISTICS ON MALIGNANT GOITER

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IN A previous paper on the occurrence of thyroid cancer (23), it was shown that clinical data, mortality tables, and autopsy statistics were in excellent agreement on this subject. It was concluded that thyroid cancer represented ½ per cent of all cancer. At current rates, this means that in a community with a population of 1,000,000 there will be about 25 patients with thyroid cancer at any time, and 1 new case will be diagnosed per month. About 6 deaths per year from thyroid cancer can be expected; autopsy might be performed in 1 or 2 of these.

At first glance it would appear that surgical statistics on the incidence of malignancy in nodular goiter are in sharp conflict with these conclusions. Reports have appeared from many centers that as many as 10 or 15 per cent of extirpated nontoxic nodular goiters contain cancer. Since nodular thyroids are relatively common even in "nongoitrous" areas, such statistics seem to indicate an incidence of thyroid cancer many times higher than 1 case per month per million population. A number of attempts have been made to resolve this apparent discrepancy. Authors who believed thyroid cancer to be common have "explained" why it appears to be a relatively rare cause of death. Others, who believed it to be rare, have tried to account for the "too frequent" diagnosis of thyroid cancer in surgical specimens. There has been much discussion of the difficulties of making a diagnosis of thyroid cancer. Most of these discussions and explanations have not been very convincing.

The aim of this study was to determine whether a discrepancy between surgical statistics and other types of data really existed and, if it did, to define the area of controversy as precisely as possible. It has been very gratifying to discover that there is in fact no discrepancy between the incidence of thyroid cancer suggested by surgical reports and the figures previously reached from study of other types of data.

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INCIDENCE OF THYROID CANCER CALCULATED FROM SURGICAL DATA

In order to compare surgical statistics with the material previously published, it is necessary to express the former in one of two ways: (a) thyroid cancer as a percentage of all cancer, or (b) incidence of thyroid cancer per unit of population per year. Most papers on thyroid cancer do not indicate how many other cancers were treated at the reporting institution, so the former expression cannot be used. The latter can be achieved in an approximate way, however, if an estimate can be made of the size of the population served by a reporting institution. Most reports indicate the period of time during which the data were accumulated, so that the number of thyroid cancers per year is easily calculated. Table I presents statistics for a number of well known hospitals in various parts of the United States. Thyroid cancer is seen to be a relatively rare disease.

It is difficult to define the population base represented by statistics from a particular hospital. For some institutions with a large "referred' practice and with sufficient popular fame to draw self-referred patients from great distances, it is impossible. Such centers have, therefore, been excluded from these calculations. The following method was used to obtain an approximation of the size of the population served by the remaining institutions. The percentage of the total general hospital admissions in its state, accounted for by a particular hospital, was determined from the appropriate figures published by the American Medical Association Council on Hospitals and Education. This percentage was then applied to the population of the state to obtain the population base for the hospital in question. Obviously, this is a very crude way of determining the size of the population represented by a series of thyroidectomies at a particular

hospital. However, it is the best simple method I could devise. Figures derived in this way are more likely to be accurate if the data from several large hospitals in an area are pooled. As fewer hospitals are included, the chance that the results will be grossly inaccurate increases.

Table II lists the incidence of thyroid cancer calculated by the method just described from various surgical reports. Except for the Michigan statistics, population and admissions figures for the census years 1940 and 1950 were used for these calculations, the year closest to the midpoint of the period covered by a particular paper being used for the data in that paper. The calculations for Michigan were based on the 1920 population and the 1931 admissions figures. The latter was the earliest year for which the necessary figures could be found. Where data from more than one hospital in a state were available, they were pooled in order to increase the reliability of the result. The calculated incidence ranges from 0.5 to 5.3 cases per 100,000 population per year. It is probably significant that the extremes of this range are found among the smallest population bases (where the results would be expected to be less accurate). The aggregate, 2.2 per 100,000 population per year, is significantly, but not strikingly, higher than the incidence previously reported, 1.3 per 100,000 per year. Possible reasons for this moderate discrepancy will be discussed later.

TABLE I. — SURGICAL STATISTICS ON OCCURRENCE OF THYROID CANCER.

Institution and reference	Period	Thyroid cancer Average No. cases per year
Mayo Clinic, Rochester, Minn. (1, 18)	1907–47	26.5
Cleveland Clinic, Cleveland, O. (9, 20)	1922–33, 1947–52	19.1
Mass. Gen. Hosp., Boston, Mass. (7)	1937–48	9.8
Ochsner Clinic, New Orleans, La. (3)	1942–49	7.3
Univ. Mich. Hosp., Ann Arbor, Mich. (6)	1912–27	6.0
Univ. Penn. Hosp., Philadelphia, Pa. (14)	1933–44	5.4
Illinois Research Hosp., Chicago, Ill. (5)	1936–48	4.5
Georgetown Univ. Med. Center, Washington, D. C. (4)	1941–50	3.9
Univ. Calif. Hosp., San Francisco, Calif. (12)	1935–47	3.8
St. Vincent's Hosp., Los Angeles, Calif. (16)	1940–50	3.6
Swedish Hosp., Seattle, Wash. (10)	1942–51	3.3
Michael Reese Hosp., Chicago, Ill. (27)	1930–48	2.9
North Carolina Baptist Hosp., Winston-Salem, N. C. (13)	1941–45	2.7
Philadelphia Gen. Hosp., Philadelphia, Pa. (19)	1936–46	2.4
Mercy Hosp., Pittsburgh, Pa. (11)	1933–49	2.4
New Haven Hosp., New Haven, Conn.	1923–52	2.3
St. Thomas Hosp., Nashville, Tenn. (22)	1930–50	2.0
Univ. Oklahoma Hosp., Oklahoma City, Okla. (26)	1942–47	1.8
Vanderbilt Univ. Hosp., Nashville, Tenn. (17)	1925–47	1.0

INCIDENCE OF MALIGNANCY IN NODULAR GOITER

The number of cancers among nontoxic nodular goiters coming to surgery can form the basis for generalization to the community as a whole, only if it is known how many such goiters were *not* operated upon. It is to be expected, in any community receiving adequate medical care, that the great majority of all cancers will appear among surgical statistics—even if only as biopsies. However, it is known that this is not true of benign nodular goiters, the majority of which do not reach the operating room. Anyone wishing to calculate the incidence of malignancy among goiters must, therefore, divide the number of cancers by the sum of the number of goiters operated on and the number not operated on. Lacking the latter figure, this incidence cannot be calculated. The surgical data would, nevertheless, have considerable value if statistics were given for each of several strictly defined preoperative diagnostic categories. However, these figures have very little meaning when given, as they usually are, for an uncertain mixture of known cancer, suspected cancer, apparently benign goiter with pressure symptoms, goiters removed for cosmetic reasons, and nodules removed as "cancer prophylaxis."

From the data in Table II one can calculate an upper limit for the possible incidence of malignancy in nodular goiter, if an estimate can be made of the frequency of such goiter in the various communities represented. If we multiply the number of admissions by this frequency, we arrive at the number of nodular goiters among patients admitted during the year. This number can be compared with the

TABLE II. — INCIDENCE OF THYROID CANCER, CALCULATED BY STATES FROM SURGICAL STATISTICS

Institution and reference	Annual admissions		Population represented*	Thyroid cancer	
	No.	Per cent of gen. hosp. adm. in state		Cases per year	Incidence†
California					
Univ. Calif. Hosp., San Francisco (12)	7,608[a]	1.3	87,000	3.8	
Wadsworth Hosp., Los Angeles (2)	22,296[b]				
St. John's Hosp., Santa Monica (2)	6,353[b]	3.4	354,000	6.1	
St. Vincent's Hosp., Los Angeles (16)	9,224[b]				
Total			441,000	9.9	2.2
Connecticut					
New Haven Hospital	10,265[a]	7.0	120,000	2.3	1.9
District of Columbia					
Georgetown Univ. Med. Center (4)	12,210[b]	9.3	74,000	3.9	5.3
Georgia					
Archbold Mem. Hosp., Thomasville (25)	2,398[a]	1.5	46,000	0.2	0.5
Illinois					
Illinois Research Hosp., Chicago (5)	5,475[a]	3.6	281,000	7.4	2.6
Michael Reese Hosp., Chicago (27)	17,609[a]				
Michigan					
Univ. Mich. Hosp., Ann Arbor (6)	21,552[c]	8.4	307,000	6.0	2.0
North Carolina					
N. C. Baptist Hosp., Winston-Salem (13)	3,606[a]	1.8	65,000	2.7	4.2
Oklahoma					
Univ. Okla. Hosp., Oklahoma City (26)	5,420[a]	4.7	109,000	1.8	1.7
Pennsylvania					
Univ. Penn. Hosp., Philadelphia (14)	8,562[a]				
Philadelphia Gen. Hosp., Philadelphia (19)	26,034[a]	7.1	700,000	10.2	1.5
Mercy Hosp., Pittsburgh (11)	12,843[a]				
Tennessee					
St. Thomas Hosp., Nashville (22)	5,667[a]	8.7	254,000	3.0	1.2
Vanderbilt Univ. Hosp., Nashville (17)	6,295[a]				
Washington					
Swedish Hosp., Seattle (10)	13,877[b]	4.2	101,000	3.3	3.3
Aggregate			2,398,000	52.0	2.2

*Per cent of general hospital admissions in state × population of state
[a] 1940 admissions and population figures
[b] 1950 admissions and population figures
[c] 1931 admissions figures; 1920 population (see text)
†Cases per 100,000 population per year

number of thyroid cancers seen per year. Such a calculation yields a figure which is higher than the actual incidence of malignancy, because (a) some thyroid cancers do not arise in nodular goiter, and (b) many individuals with nodular goiter are never hospitalized, but almost all individuals with thyroid cancer are admitted to a hospital at some point in their course. Thus the ratio we calculate, all thyroid cancer/hospitalized nodular goiter, is higher than the ratio we want to know, malignant nodular goiter/all nodular goiter.

Jaffe found 236 nodular goiters among 1,000 autopsies in Chicago. His data indicate an incidence of nodular goiter of about 20 per cent, for a standard population in this goitrous community. Schlesinger, Gargill, and Saxe reported that at least 112 of 1,371 patients studied at autopsy in Boston had thyroid nodules 1 centimeter in diameter or larger. Their data suggest an incidence of 5.5 per cent for a standard population in a nongoitrous community. Tables IIIa and IIIb present calculations based on these figures, for Chicago and Philadelphia. It was assumed that the data of Schlesinger and associates are applicable to Philadelphia. Table IIIc presents calculations based on 30 years' experience at the New Haven Hospital, again assuming a frequency of nodular goiter equal to that in Boston. Here the material is presented somewhat differently because of the availability of additional data. Four hundred thousand patients have been examined on the wards or in the clinics of the New Haven Hospital

during the period 1923 to 1952. Seventy of them were found to have thyroid cancer. Of these, 13 are known not to have had nodular goiter. The remaining 57 are either known to have had nodular goiter, or definite information is not available; they have all been counted as having nodular goiter. These statistics are believed to be especially significant because they deal with patients rather than admissions, and because of the long follow-up of many of these individuals (including autopsy in 10,000 of them). The results for these three communities check quite well and indicate an upper limit of about 0.3 per cent for the incidence of malignancy in nodular goiter.

TABLE III.—INCIDENCE OF MALIGNANCY IN NODULAR GOITER

		No. per year
a.	Chicago, Ill. Pooled data from two general hospitals (5, 27)	
	Total admissions	23,000
	Nodular goiter (estimated)	4,600
	Thyroid cancer found	7.4
	Per cent of nodular goiter	0.2
b.	Philadelphia, Pa. Pooled data from two general hospitals (14, 19)	
	Total admissions	35,000
	Nodular goiter (estimated)	1,900
	Thyroid cancer found	7.8
	Per cent of nodular goiter	0.4
c.	New Haven, Conn. New Haven Hospital, 1923–1952	
	Patients examined	400,000
	Nodular goiter (estimated)	22,000
	Thyroid cancer found	70
	Nodular goiter not present	13
	Malignant nodular goiter	57
	Per cent of nodular goiter	0.3

DISCUSSION

The institutions listed in Tables I and II are leading hospitals in their respective communities. Also, many of them are institutions where some special interest is taken in thyroid cancer. For both these reasons it is likely that they admit somewhat more than their proportionate share of this interesting and relatively rare disease. This probably occurs through an increased number of primary admissions of thyroid cancer as well as through referrals for additional therapy of patients initially treated elsewhere. At the New Haven Hospital there is almost a two-fold concentration of thyroid cancer, as compared with the state of Connecticut as a whole (23). This degree of selection is sufficient to account for the slight discrepancy between the aggregate incidence in Table II of 2.2 thyroid cancers per 100,000 population per year and the figure of 1.3 per 100,000 per year previously arrived at, in an analysis of more comprehensive statistics of other types.

The agreement between the statistics discussed in this paper and those previously reviewed is not surprising. Most diagnoses of cancer are, after all, based on reports from surgical pathologists. Thus, surgical statistics on any form of cancer should agree with summaries of clinical cancer experience. And unless surgical pathology reports are grossly inaccurate, such statistics should be confirmed by death certificates and autopsy examinations. This was shown to be true of thyroid cancer (23).

Mortality and autopsy statistics fail to reveal any major inaccuracy in the diagnosis of thyroid cancer from surgical specimens. Undoubtedly, occasional erroneous diagnoses are made in this, as in other diseases. However, although there has been much argument over the criteria for a histologic diagnosis of thyroid cancer, no evidence has been presented that competent pathologists would disagree to any great extent over the interpretation of an average set of slides of thyroid tissue. In an investigation of one phase of this problem, Perloff and Schneeberg found excellent agreement among 7 pathologists over the diagnosis of thyroid cancer, although there was some disagreement as to whether certain slides represented primary or metastatic disease. In retrospect, it appears to this nonpathologist that borderline histologic sections and quantitatively unimportant points of disagreement have received far too much emphasis in discussions of this problem by authors who hoped to resolve what appeared to be a serious discrepancy between different types of statistics.

The question may be raised whether the exclusion of statistics from certain institutions may have distorted the calculations in this paper. There are about 2,000 new cases of thyroid cancer diagnosed per year in this country. The Mayo Clinic, Cleveland Clinic, Lahey Clinic, Memorial Hospital, Massachusetts General Hospital, Johns Hopkins Hospi-

tal, and Ochsner Clinic together account for less than 5 per cent of that number. None of the hospitals listed in Table II are in the same states as these institutions. It is unlikely, therefore, that the relatively high concentration of thyroid cancer at these centers reflects any significant diversion from those hospitals.

Table III gives indirect calculations of an upper limit for the incidence of malignancy in nodular goiter. The weakest elements in these calculations are the estimates of the incidence of nodular goiter in the various hospital populations. These estimates are based on 2 autopsy studies, neither of which is ideal for our purpose. Jaffe counted all nodules discovered on sectioning the thyroid glands. Undoubtedly, many of these were not palpable during life. The incidence of thyroid nodules reported by Jaffe may thus be considered as a "ceiling" for the incidence of *palpable* nodular goiter. And it is quite likely that cancer is more prevalent among palpable nodules than among those not clinically detectable. Fortunately, a "floor" is available for comparison with Jaffe's data. Crile and Dempsey (8) reviewed a series of consecutive clinical charts at the Cleveland Clinic, excluding patients with a complaint of thyroid disease and patients to whom thyroid surgery was recommended, and found that 4 per cent of the remainder were recorded as having symptomless nodular goiter. Thus it may confidently be said that the incidence of palpable nodular goiter in the Great Lakes area is more than 4 per cent and less than 20 per cent. If Table IIIa were recalculated on the basis of an intermediate figure of 10 per cent, the upper limit for the incidence of malignancy in nodular goiter would turn out to be 0.3 per cent.

Schlesinger and associates, whose data were used for Philadelphia and New Haven, counted only glands described in autopsy protocols as having nodules at least 1 centimeter in diameter. Glands with smaller nodules, or with nodules whose size was not stated, were not counted as nodular. It is reasonable to conclude that the figures reported by these authors represent clinically detectable nodules. However, these figures were not derived from consecutive autopsies. The 1,371 glands constituting the sample came from 2,185 autopsies. It is quite likely that there was less nodular goiter among the 814 glands not examined than in the sample reported upon. Recalculation of Tables IIIb and IIIc, using two-thirds of the incidence of nodular goiter reported by Schlesinger and associates (this implies that there was *no* nodular goiter among the autopsies in which the thyroid was not examined—a rather unlikely hypothesis), would yield figures of 0.6 and 0.4 per cent, respectively.

As has been emphasized, hospital statistics contain a "concentration" of thyroid cancer relative to benign nodular goiter. It is unlikely, therefore, that for the population as a whole the incidence of malignancy in palpable nodular goiter would be as high as 0.5 per cent. This conclusion is consistent with that reached in another analysis of this problem (24).

It would be desirable, of course, to have direct rather than indirect evidence on this important subject. As Crile and Dempsey have pointed out, there are many echelons of selection operating to weed out the less suspicious thyroid nodules, before patients with nontoxic nodular goiter are operated upon. An example of the degree of selection taking place even at the final stage of the process these authors described may be seen in the experience of the Ochsner clinic (3). Five hundred and eighty nodular goiters were seen over a 7 year period. Most of the patients were referred, some with the histologic diagnosis of thyroid cancer already established. Excluding these known cancers, there were 252 thyroidectomies. Cancer was demonstrated in 43, or 17 per cent of these. For various reasons, thyroidectomy was not performed in 320 patients. None of these are known to have developed evidence of thyroid cancer during a follow-up period of 1 to 7 years. This experience demonstrates that it is possible to select "low-risk" and "high-risk" groups of nodular goiter. It is of some interest that these results were reported from an institution where thyroidectomy is recommended for *all* nodular goiter. Obviously, statistics derived from a "high-risk" group are not applicable to nodular goiter in general.

An important type of selection not discussed by Crile and Dempsey may be observed in some communities where a well known thyroid

surgeon believes that all nodular goiters should be removed. It will be noted in such communities that many internists and general practitioners will refer patients to this surgeon if they believe that there is serious risk of malignancy in a goiter, but will send patients to some other consultant, who does not subscribe to this doctrine, for confirmation of their opinion that a goiter is benign and may be watched. This type of selection may be largely responsible for the extraordinarily high incidence of malignancy which has been reported by some surgeons who are famous both for their technical competence and for their belief that in all instances nodular goiters should be extirpated.

The various types of preoperative selection apparently operate quite efficiently at large metropolitan centers, and it would be hopeless to look for valid direct evidence from such communities. In a relatively isolated rural community, on the other hand, it might be possible to accumulate suggestive statistics on this point, if all of the physicians practicing in the area recommend thyroidectomy for all nodular goiter. In such a community there would be only one echelon of selection—the patient himself. Some residents of the community with asymptomatic nodular goiter would not be under medical care and thus would not be included in a thyroidectomy series. Others might refuse a recommended operation. However, the degree of selection would be considerably less than in a large metropolitan center. Watt and Foushee have reported what may be a close approximation of such an ideal experimental situation. Their experience covers 25 years in a rural community in southwest Georgia. Thyroidectomy was performed in all cases of nodular goiter. In addition to 3 obvious, advanced cases of thyroid cancer, these authors operated upon 272 nodular goiters. Only 1 per cent of these proved to be malignant. Watt and Foushee commented on the discrepancy between their statistics and those from many large medical centers and emphasized the very much smaller factor of selection in their community. It is particularly unfortunate that this significant report has not received the attention which it deserves.

SUMMARY AND CONCLUSIONS

Surgical statistics on thyroid cancer have been reviewed. The incidence of this disease calculated from surgical reports agrees satisfactorily with the figure previously published, approximately 1 new case per month per million population. All available statistics on the incidence of thyroid cancer have now been shown to be in good agreement.

There is no evidence that erroneous histologic diagnoses of thyroid cancer are made with undue frequency. It is suggested that disagreements among pathologists over difficult or borderline cases may have been unduly emphasized in some discussions.

It is possible to divide nodular goiters clinically into high-risk and low-risk groups, insofar as the possibility of cancer is concerned. The figures usually cited for the incidence of malignancy in nontoxic nodular goiter are drawn from selected high-risk samples and are not applicable to the general population. The incidence of malignancy among *unselected* nodular goiters is less than 0.5 per cent.

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The Assault at Okinawa, Easter Sunday Morning, 1945

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EDITORIAL

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JULY, 1954

THE TREATMENT OF SECONDARY TUMORS OF LUNG

RECENT developments in all aspects of the care of surgical patients have greatly increased the scope of the operations which may be done for advanced malignant disease. The widening horizons have brought new responsibilities for surgeons. No longer does the surgeon direct his judgment only to the questions of whether a tumor can be excised beyond its visible limits and whether the patient can support such an operation; very often he must look beyond the technical problem and decide not only can the operation be done, but should it be done. He is conscious of the fact that he is attempting to solve what is essentially a biologic problem by a crude physical method and that in the case of extensive tumors there will be many failures.

In such a situation a surgeon must call on all his wisdom and experience. He must know the natural history of tumors, what is the cause and manner of death if nature takes its course, and how this can be modified by palliative treatment, either surgical, radiotherapeutic or chemotherapeutic. He must remember the pain and suffering which accompany major operations. He must realize that many of these patients have only weeks or months to live and consider how they should be spent to the best advantage. He must think of the expense of hospital care. If encouraged to do so, a family will uncomplainingly sacrifice all its resources in a fruitless attempt to save a life.

Against this must be placed the fact that a small proportion of patients with advanced cancer appear to be cured by extensive operations undertaken in the face of the most discouraging conditions. The patient has a different point of view from the doctor. The conscientious surgeon is oppressed by thoughts of percentages and a preponderance of failures; the patient thinks only of his own problem and usually wants to have his chance for cure even though the odds are heavily against him. A doctor's duty is not only to cure disease but also to prolong life and relieve suffering. Many malignant tumors will cause death or disability by interference with a vital organ or function long before the patient would succumb to disseminated tumor. There is a place for palliative surgery; a few months or years of comparative health and gainful employment may be an ample reward even for an arduous surgical experience.

To take into account all these factors and reach a wise decision on the problem presented by an individual patient requires more than a mere knowledge of the potentialities of surgical technique; it requires a broad under-

standing of malignant disease and a sympathetic assessment of the patient as an individual and in relationship to his family.

It is in the light of some of these considerations that one must weigh the merits of attempting to cure a patient of malignant disease by excising a metastatic lesion of lung. Until recently the demonstration of a secondary tumor in the lung was accepted as categorical evidence of incurability but there are now a considerable number of case reports in the literature describing survival for long periods after excision of such tumors. This indicates that, occasionally, a single metastatic tumor may represent the only residuum of disease after successful treatment of the primary lesion, but from what we know of the nature of tumors we must expect that more often the apparently solitary lung tumor will prove to be only the big brother of smaller and still unrecognized members of a family of metastases.

It is difficult to assess the survival rate after this form of treatment. There are now some 70 cases reported, but there are so many variables in respect to the nature of the primary tumor and the method of reporting that one can reach only the most general conclusions. By taking into account only those cases which are reported as failures within 3 years and the cases of patients reported as alive without evidence of recurrence at 3 years or longer, it is apparent that about 30 per cent of the patients fall into the latter category. This figure may be quite misleading because it is probable that successful cases have been reported more often than failures. If the figure means anything it suggests that the survival rate after excision of an apparently solitary secondary tumor of lung is comparable to that after pneumonectomy for a primary lung tumor. On that basis the treatment merits consideration at least.

There is little to guide us in the selection of cases. Almost every type of tumor which is capable of metastasizing to the lung has been treated in this manner. Curiously enough the sarcomas appear to have given a little better results than the carcinomas. It is natural to expect that the longer the interval between the treatment of the primary tumor and the appearance of the metastasis the greater the hope of success, but this is not borne out by the limited information available.

Little is known about the relative tendency of secondary tumors to give rise to a further generation of what might be called "tertiary" tumors, but it does appear that these are less likely than the parent primary tumor to metastasize along lymphatic channels so that a restricted operation, usually a lobectomy, is adequate. Secondary tumors, on the other hand, can and do invade blood vessels and have the capability of hematogenous dissemination. For that reason, if excision of the secondary tumor is to be considered at all, a decision should be made and the operation performed, rather than waiting to see if further tumors appear in the lung or elsewhere.

Finally, when a patient who has been treated for a malignant tumor develops a lesion in the lung, it cannot be assumed that it is necessarily a secondary tumor. It may be a primary lung tumor or some other condition amenable to treatment and should be properly investigated. If, after investigation a doubt remains, the patient should receive the benefit of surgical therapy.

At the Toronto General Hospital our experience to date is somewhat encouraging. Of 9 patients who have been treated for a secondary tumor of lung by total or partial pneumonectomy 6 are alive without evidence of recurrence, although 3 of these have been observed for a very short time only. The types of primary tumor and the survival periods are

as follows: fibrosarcoma of thigh 6½ years, carcinoma of the sigmoid colon 4 years, acantho-adenocarcinoma of uterus 3 years, malignant melanoma 18 months, carcinoma of vagina 3 months, chorionepithelioma 1 month. Two patients died after 1 year with further metastases, the primary tumors being renal and breast carcinoma, and 1 patient is alive at 4 months with known metastases after a pneumonectomy for a large tumor secondary to carcinoma of the rectum.

From the evidence available one may conclude that when a patient develops an apparently solitary metastasis in the lung and there is a reasonable expectation that the primary tumor has been eradicated, based on the passage of time or the pathologic characteristics of the primary tumor, or both, then surgical excision of the secondary tumor should be considered and recommended if other factors appear to be favorable. It is important that surgeons continue to report their results, the disappointing as well as the gratifying, so that a more accurate assessment may be made of the value of the treatment and in the hope that some criteria may be developed to assist in the selection of the more favorable cases.

FREDERICK G. KERGIN.

THE SURGEON AT WORK

THE STERILE SCALPEL

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THE scalpel is the single instrument characteristic of surgery. Surgeons demand that it be both sharp and sterile. Current hospital techniques for the disinfection or sterilization of cutting-edged instruments are often bacteriologically unreliable and destroy the keenness of the cutting edge.

Dulling of the surgical blade occurs by mechanical contact during processing essential to preparation for the aseptic field. It has been customary to coat the detachable blade with a protective film of oil to prevent atmospheric corrosion during storage. The removal of this material to enable disinfection exposes the blade to dulling. Some manufacturers package the blade in corrosion-inhibiting paper to obviate this step prior to immersion in a corrosion-inhibiting germicide. Special containers for germicide are obtainable in which the blade is suspended during disinfection to avoid dulling contacts. Dry heat sterilization at 320 degrees F. (160° C.) for 1 hour is employed in some hospitals. Overheating, as well as the handling entailed, results in destruction of the cutting edge.

A unique package solves these problems economically, brings convenience to the surgeon and safety to the patient. The perfectly sharpened scalpel blade, appropriately cleaned, is hermetically sealed in an aluminum foil packet prior to sterilization. The packet can be opened by pulling apart two tabs which expose the sterile blade for instant use (Figs. 1 and 2).

Sterilization of the sealed packet is accomplished by exposure to dry heat for a period sufficient to destroy microbial life. Sterility of each lot of packets is proved by culture of random samples in accordance with the techniques described in the *Pharmacopoeia of the United States*, Volume XIV, page 758.

Random samples of two separately sterilized lots of 100 packets each were selected. Each packet was opened separately by peeling back the tabs to expose the blade which was spilled at once into a culture tube containing 40 milliliters of medium. Ten blades were tested in each of the recommended media, fluid thioglycollate medium U. S. P., Sabouraud liquid medium, (modified) U. S. P., and peptone broth medium U. S. P. Each medium was tested for its growth promoting and oxidation-reduction qualities using bacteria known to be exacting in growth requirements. The sterility of each lot of sterilized test medium was confirmed. The cultures in fluid thioglycollate medium U. S. P. and in peptone broth medium U.S.P. were incubated at 32 to 35 degrees C. for 15 days. Cultures in the Sabouraud liquid medium (modified) U. S. P. for molds and yeasts were incubated at 22 to 25 degrees C. for 15 days. There was no macroscopic evidence of growth and microscopic examination of stained smears disclosed no micro-organisms. The oxidative effect of the media on blades did not result in significant change in the color of the indicator dye which was present.

The possibility of interference with bacteriologic testing as the result of the oligodynamic action of the metal was investigated. Half of the culture tubes containing fluid thioglycollate medium (modified) U. S. P. were inoculated with 1 milliliter of a 1:100,000 dilution of an 18 to 24 hour fluid culture of Clostridium novyi; and were incubated for an additional 3 days at 32 to 35 degrees C. The remainder of the tubes containing fluid thioglycollate medium (modified) U. S. P. were inoculated with 1 milliliter of a 1:100,000 dilution of an 18 to 24 hour fluid culture of Escherichia coli and were incubated for an additional 3 days at 32 to 35 degrees C. All of the culture tubes containing peptone broth were inoculated with 1 milliliter of a 1:100,000 dilution of an 18 to 24 hour fluid culture of Escherichia coli and were incubated for an additional 3 days at 32 to 35 degrees C. All of the culture tubes containing Sabouraud liquid medium (modified) were inoculated with 1 milliliter of a 1:1,000 dilution of a 72

From the Departments of Pathology and Surgery, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts.

Fig. 1.

hour Sabouraud liquid medium (modified) culture of Candida candida and were incubated for an additional 3 days at 22 to 25 degrees C. There was no macroscopic failure of microbial growth or perceptible inhibition in any of the inoculated tubes. Microscopic examination of stained smears showed the organisms to have essentially the same appearance as in control cultures containing no surgical blades. The viability of the several test organisms was also confirmed by subculturing at the end of the 3 day period.

The blade is dispensed to the aseptic field by the circulating nurse. She grasps a tab of the packet in either hand, pulls them apart to break the seal, and peels the sides of the packet back to expose the blade which is then spilled on to the aseptic field (Fig. 3). Because sterile, sharp blades are thus instantly available, they can be dispensed as needed by the surgeon. This avoids the conventional but wasteful preparation of several blades for each operation.

The economies in time and reduction in waste of blades are obvious. The technique eliminates the inconvenience and expense of maintaining containers of germicide or dry heat sterilizers. Transfer forceps with their inherent hazards are unnecessary.

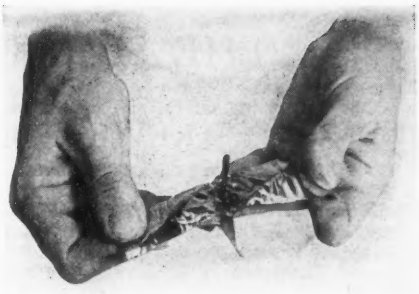

Fig. 2.

Fig. 3.

The convenience and safety of this technique are singularly advantageous in office practice and in military use. An assortment of sterile blades can be carried in the physician's bag to use at the bedside.

CONCLUSION

A unique method of packaging sharp surgical blades is described.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE first edition of *Lehrbuch der Geburtshilfe*, prepared by Koller and 9 Swiss associates, was published in 2 volumes and contained a total of 1,323 pages. The 9 authors of this edition agreed to shorten the book to keep the price down and limit the book to essentials only. The book[1] now is in one volume and contains 907 pages. Koller laments the fact that the illustrations also had to be cut. There is a drastic reduction from 711 illustrations in the first edition to only 348. This is really regrettable because many drawings and photographs are absolutely essential for textbooks prepared for students. In this book the curtailment of illustrations is distinctly unfortunate because now 96 of the entire 348 illustrations (constituting 28 per cent) are devoted to the subject of fetal monsters and abnormalities.

The subjects covered are: (1) human embryology and morphology of the newborn, (2) normal pregnancy, (3) normal labor, (4) the puerperium, (5) physiology of the newborn, (6) multiple pregnancy and labor, (7) breech presentation, (8) pathology of pregnancy, (9) extrauterine gestation, (10) dystocia, (11) pathology of the puerperium, (12) fetal monsters, and (13) pathology of the newborn.

It is gratifying to note that the authors heeded several criticisms made of the first edition. They have omitted the illustrations of Credé's expression of the placenta and of Schultze's heroic swingings to resuscitate newborn babies and they markedly reduced the number of pages devoted to fetal monsters and pathology of the newborn, although these sections are still too large. Generally the allotment of space is uneven. The section pertaining to erythroblastosis is most inadequate. Amniotic fluid embolism is not mentioned; neither is the lower nephron syndrome.

As in the first edition, the advice given throughout the book is in accord with the conservative teaching of obstetrics in most parts of the world. The illustrations which have been retained are all clear and instructive. The type is clear, but there is too much data in tiny type. The quality of the paper is good. This edition deserves to be even more popular than the first because it constitutes one of the best textbooks written on the subject of obstetrics which has been published in any language. J. P. GREENHILL.

[1]LEHRBUCH DER GEBURTSHILFE. By Prof. Dr. E. Held, Dr. O. Kaeser, Prof. Dr. Th. Koller, Dr. A. Reist, Prof. Dr. H. Schultheiss, Prof. Dr. R. Wenner, Prof. Dr. A. Werthemann, Prof. Dr. H. Willi, and Prof. Dr. G. Wolf-Heidegger. 2nd rev. ed. Basel: S. Karger, 1953.

A concise, practical outline of the everyday phases of regional analgesia is presented in *Regional Block; a Handbook for Use in the Clinical Practice of Medicine and Surgery*.[2]

The materials and techniques are those used by the author and found to be the simplest and most satisfactory. It is designed for the beginning anesthesiologist and the general practitioner or surgical specialist who may be called upon to furnish his own anesthesia, diagnostic, or therapeutic block. The material is very well organized so that it is easy to study a particular block, step by step, without reading through the entire book.

Part 1 is a discussion of fundamental principles, Part 2 deals with nerve blocks, and Part 3 with spinal subarachnoid and caudal (epidural) anesthesia.

Less frequent procedures and those with a high incidence of serious complications are very wisely omitted. For each procedure the author first discusses the indications, then anatomy, and following this, premedication, drugs, and materials, techniques which include positions and landmarks, precautions, and procedures. Following this is a discussion of the extent of anesthesia, complications, and corrective measures and remarks.

This is an excellent book and will be greatly appreciated by anyone who at times is obliged to furnish his own anesthesia. This reviewer would have been grateful many times for such an aid and guide during his services in World War II. It should become a part of every surgeon's library.

RUSSELL T. BOTHE.

THE third edition of *Pediatric Gynecology*[3] is of special value to the general practitioner and pediatrician, for it covers the diagnostic and therapeutic problems of the genitourinary tract of the female infant and child.

There is a short chapter on the embryology of the female genital system which is fundamental to an understanding of the various congenital abnormalities. The special methods of investigation are presented in detail—methods of examination, including vaginoscopic examination and the technique of vaginal smears and culture.

[2]REGIONAL BLOCK; A HANDBOOK FOR USE IN THE CLINICAL PRACTICE OF MEDICINE AND SURGERY. By Daniel C. Moore, M.D. 373 pages, with 262 illustrations. $11.00. Springfield, Ill.: Charles C Thomas, 1953.

[3]PEDIATRIC GYNECOLOGY; WITH SELECTIONS ON UROLOGY AND PROCTOLOGY. By Goodrich E. Schauffler, M.D. 3rd ed. 318 pages, 76 illustrations. $7.50. Chicago: The Year Book Publishers, Inc., 1953.

Vaginitis is thoroughly discussed, and abnormalities of the immature breast and menstrual disorders of the adolescent are thoroughly delineated. There are chapters on general surgical consideration, urologic problems of the female child, and a chapter on proctology.

This is a useful volume which will prove of real worth to those who care for children.

DENNIS H. KELLY.

THE book *Peptic Ulcer; Pain Patterns, Diagnosis, and Medical Treatment*[1] is designed to be of aid in the accurate diagnosis and satisfactory medical management of peptic ulcer. The authors have had an extensive experience in the treatment of these diseases at the Mayo Clinic, and have analyzed this large body of data in a most useful manner. There is an excellent discussion of the varieties of peptic ulcer, their symptomatology, and differential diagnosis. The physiology of gastric secretion and its relation to the etiology of peptic ulcer is outlined. The symptomatology of esophageal ulcer, gastric ulcer, and duodenal ulcer is outlined with reference to the pain patterns involved. A chapter on the endoscopy of the stomach is provided by Herbert W. Schmidt, and a chapter on roentgenologic diagnosis by C. Allen Goode. Detailed directions are given for the medical management of peptic ulcer and the importance of co-operation on the part of the patient in successful therapy is emphasized. This book should prove most useful to gastroenterologists and, indeed, to all physicians who are called upon to treat this common disease.

LESTER R. DRAGSTEDT.

THE book *Surgery of Trauma*[2] represents a very ambitious and worthwhile project—that of presenting the many facts concerning wound healing and correlating the clinical facts as applied to trauma of the various systems and organs. The author has been able to draw upon well known and recognized authorities in all the fields of trauma, encompassing a wide experience gained in World War II and in the Korean conflict.

Actually this text is concerned with war type injuries, and each anatomic region and organ of the body is well covered. Clinical problems such as shock, burns, and infections are also included.

This volume seems almost too ambitious, for while some chapters confine themselves to the acute phase of injury, others are too long and include later reconstructive surgery rather needlessly, for all of the latter is already well documented in current surgical texts.

The initial part of the book deals with wound healing—first the general factors, and then healing of specific tissues and organs; the metabolic response of the body to a wound, the shock state, and infections. Section 2 is devoted to regional wound surgery, but the presentation is not always consistent. For example, the chapter on wounds of the spinal cord is concise, well illustrated, and deals with first aid, evacuation, organization of the service, and indications for surgery. There are other excellent chapters on the chest, abdomen, and on fractures. The remaining chapters are not of lesser quality, but are not confined to the acute phase, with emphasis on what to do and when to carry out certain procedures. Too much space is devoted to late reconstructive surgery.

This text is a much needed addition to our surgical libraries, but it might well have been restricted to acute combat conditions, and situations produced by a catastrophe, by considering care of the wounded patient up to the period of late reconstructive surgery.

Section 3, military considerations, is pertinent but could be placed earlier in the volume. There is considerable repetition of previous chapters, as for example the section on infections. It is confusing to the reader to find local care of the burn wound, of burn shock, and of burns of the hands scattered throughout three different sections.

This volume assembles in permanent form and consolidates the knowledge gained from the care of war wounds. In the future surgeons can turn to it for careful and well founded guidance, whether for preparation for a tour of combat or in the event of a catastrophe. With such aid they will not need to depend on the more limited experience of civilian life when faced with the responsibility for caring for a large number of patients with serious, and often multiple as well as unusual injuries.

HARVEY S. ALLEN.

THE authors of *An Atlas of Pelvic Operations*[3] have set about to present the technical details of pelvic surgical procedures as they use them in the institution in which they work. They have chosen to describe single standard procedures, rather than to present multiple types of procedures for each situation, which is good. The book gains value by portraying the authors' own ideas instead of mulling over the thinking of everyone who has written on the subject. In this way the reader learns the methods used by the authors and the kind of gynecology that they practice. It is a good pattern for a book.

Indications are not given for the operations described, but they are purposefully omitted since the authors wished to prepare an atlas which would present only the technical details of certain pro-

[1] PEPTIC ULCER; PAIN PATTERNS, DIAGNOSIS, AND MEDICAL TREATMENT. By Lucian A. Smith, A.B., M.D., M.S. in Medicine, F.A.C.P., and Andrew B. Rivers, M.A., M.D., M.S. in Medicine, F.A.C.P. Foreword by George B. Eusterman. 576 pages, 208 illustrations. New York: Appleton-Century-Crofts, Inc., 1953.

[2] SURGERY OF TRAUMA. Edited by Warner F. Bowers, Colonel, MC, U.S.A., with forewords by Melvin A. Casberg, M.D., and others. 605 pages, 284 illustrations. $15.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

[3] AN ATLAS OF PELVIC OPERATIONS. By Langdon Parsons, M.D., and Howard Ulfelder, M.D. Illustrated by Mildred B. Codding, A.B., M.A. 231 pages, 197 plates. $18.00. Philadelphia and London: W. B. Saunders Co., 1953.

cedures. This approach is commendable, and well thought out. The book is more useful because of it.

The operative procedures given are not limited to those in gynecology, but include numerous general surgical ones as well. Those for cancer of the cervix are especially worth while. The technique of lymphadenectomy and groin dissection are excellent additions because of the more extensive operations that are now used and required in the treatment of some genital malignancies. The drawings and the accompanying word descriptions are explanatory and clear.

This atlas is a valuable addition to the library of any surgeon. Its greatest value, however, is derived from the fact that it is so prepared that it can be taken into the operating room, placed on a stand, and used in the training of the house staff and others who are desirous of learning operative procedures that have been demonstrated to be practical, sound, and safe. I shall use it in this way. The fact that each of us has other procedures which we prefer in the management of some pelvic lesions does not detract from the usefulness of this atlas, since all of us, no matter how proficient, glean some points from these descriptions that will improve our work.

JOHN BREWER.

THE collection of 24 monographs dealing with currently active and expanding phases of radiologic diagnosis entitled *Modern Trends in Diagnostic Radiology*[1] is highly authoritative since the various section authors selected by the editor have been chosen because of their valuable contributions to the particular subjects under consideration. Newness of subject matter and its treatment have been stressed.

While obstetric radiology has not been included, the sections on acute abdominal diseases, the small intestine, colon, pancreas, renal tract, lumbar aortography, and hysterography will certainly hold great interest for surgeons and gynecologists. The first of these, by Frimann-Dahl, emphasizes to what extent thoughtful planning of x-ray examination of the abdomen, coupled with alert observation, can throw important light upon otherwise obscure abdominal situations.

The sections "Cardiac Dynamics and Angiocardiography" and "Selective Angiocardiography and Thoracic Aortography" by Wegelius and Lind and by Johnsson, respectively, are truly excellent expositions dealing with radiologic procedures which are growing with great rapidity and which are providing a new understanding of circulatory mechanics and physiology.

Illustrative material is of a high quality except perhaps in the field of apparatus where simplified diagrams might have been more helpful than photographs.

FRED J. HODGES.

[1]MODERN TRENDS IN DIAGNOSTIC RADIOLOGY. 2nd series. J. W. McLaren, M.A., M.R.C.P., F.F.R., D.M.R.E. 413 pages, 359 illustrations. $18.00. New York: Paul B. Hoeber, Inc., Med. Book Dept. of Harper & Bros., 1953.

THE volume *Próteses metálicas e acrílicas nas artroplastias*[2] treats of the indications, techniques and late results in arthroplasty employing metallic and acrylic prostheses with particular reference to the coxofemoral articulation. It is based on the experience of 92 operations, in 10 of which the vitallium cup and in 82 of which the acrylic prostheses were used. In the chapter on technique each type of the more important prostheses available is portrayed and the steps employed when the vitallium cup and the acrylic prosthesis are used are illustrated in color. The author employs the Smith-Peterson incisional approach when using vitallium and the anterior Heuter when the acrylic head is used. This latter is preferred by the author inasmuch as he has had greater experience with this device.

The results are tabulated and frankly discussed with the complicating causes expressed.

Of the 82 patients, 48 were women and 34 men. The data reported extend over 4 years. Up to date there have been only 9 instances of bad results and 3 deaths, which occurred during the immediate postoperative stage. Fracture of the femoral neck (38), and pseudarthrosis (29) have been the principal surgical indications, in patients ranging from 10 to 86 years in age. It is believed that when it is not specifically contraindicated, arthrodesis is superior to and safer than any other solution of the hip problem. Chronic arthritis permits more accurate evaluation of the procedures wherever vitallium cup or acrylic prosthesis may be employed. However, the acrylics are considered simpler to handle and give better results.

The volume is nicely arranged, the author apparently has given considerable thought to the manner of presentation of his material. A summary in English, French, and German is appended and contributes in no small way to the value of the book.

STEPHEN W. ZIEMAN.

THE author of *Dystrophia Musculorum Progressiva*[3] is a professor in the Department of Psychiatry and Neurology at the University of Freiburg. His monograph is limited to muscular dystrophy, which he considers a clinical entity. His work is based on 259 cases of progressive muscular dystrophy.

The author deals primarily with the genetic derivation of the disease and was able in his study to establish that genetically there are 3 types of progressive muscular dystrophy. Each shows hereditary tendencies. These genetically established forms can also be distinguished from each other by their clinical picture.

In the clinical form one type is a direct genetic form which starts at the shoulder girdle and then

[2]PRÓTESES METÁLICAS E ACRÍLICAS NAS ARTROPLASTIAS; INDICAÇÕES—TÉCNICAS E RESULTADOS TARDIOS. Prof. F. E. Godoy Moreira. 132 pages, 65 illustrations. São Paulo, 1953.

[3]DYSTROPHIA MUSCULORUM PROGRESSIVA; EINE GENETISCHE UND KLINISCHE UNTERSUCHUNG DER MUSKELDYSTROPHIEN. By Prof. Dr. P. E. Becker. 31 pages, 101 illustrations. DM 28.50. Stuttgart: Georg Thieme Verlag, 1953.

involves the muscles of the face and later the muscles of the lower extremities. The other two types result from recessive traits, they start at the pelvic girdle and later involve the trunk and arms.

The various forms are described and the description followed by complete reports including the family history of the author's cases of progressive muscular dystrophy.

This is a scientific monograph with many tables and graphs. The author quotes extensively from the literature and gives a complete bibliography.

This monograph is essential for anyone doing investigative work in muscular dystrophy. It is of value in establishing prognosis and is an important contribution to the study of human genetics.

EMIL D. W. HAUSER.

NO one who reads the well written treatise on hand injuries entitled *Surgery of Repair as Applied to Hand Injuries*[1] but will realize very quickly that it has been prepared by men who have had wide experience in the care of such injuries and have brought skillful care and thoughtful judgment to the solution of the problems facing them. They have not been content, moreover, with the surgical care of their patients alone, but have considered the social and economic aspects of the working man's problem as well, and emphasize the importance of "following through" until the patient has returned to his job or to one which he is capable of doing.

Part 1 includes 4 chapters: "The Social Significance of Hand Injuries," "Surgical Anatomy of the Hand," "Organisation in Relation to Hand Injuries," and "Examination and Appraisal of a Recently Injured Hand." They are so concisely and so well written they could serve as required reading for every industrial surgeon and every worker in the emergency wards of our modern hospitals.

In Part 2 on "Primary Treatment" the authors emphasize so many important principles and express them so well that one cannot refrain from quoting a few of the many pertinent and well phrased comments they have made:

With reference to anesthesia, "Local anaesthesia has an invaluable place in hand surgery (but) adrenalin should never be used in the solution because of its vasoconstricting influence (in addition to the mechanical constricting effect of any injection) may adversely affect the viability of a part."

"Antiseptics are not used in the wound itself—they are harmful and unnecessary" (p. 59).

"Doubtful flaps may be left for a time at operation to see if they can improve, but if they do not they should be discarded rather than retained with optimism. We commonly hear the expression, 'We did not think the flap would live but we just sutured it back in case.' This is not the pathway to success but to disaster. The only luck one can expect is bad luck" (p. 60).

With reference to immediate repair of the deep tissues, "Fractures and dislocations must be reduced and maintained, but whether or not tendons and nerves are repaired is a different matter. Physical continuity in these structures is insufficient—they must function. They cannot function in a mass of scar tissue, so that if the highest standard of primary healing cannot be anticipated with absolute confidence the repair of tendon or nerve is generally ill-considered at the primary procedure" (p. 62). One would like to reprint in bold letters that concise phrase, "They must function." It is the essence of the problem of nerve and tendon injuries.

"Wounds should be healed before movements are commenced. Early healing rather than early movement is the immediate object of primary treatment. Early movement will follow as corollary to early healing" (p. 72).

Part 3, "Intermediate Treatment," Part 4, "Secondary Treatment of Hand Injuries," and Part 5, "Special Aspects of Hand Injury," including chapters on the "Burnt Hand," "Hand Injuries in Children," and "Hand Prothesis" detail the authors' ideas and wide experience in these fields. The numerous and excellent illustrations, and the line drawings of technical procedures add both interest and clarity to the discussion.

Anyone who is interested in the many problems involved in the surgery of the hand must agree wholeheartedly with practically everything that the authors have suggested and advised. They have made a memorable and helpful contribution which will help to raise the standards of treatment of injured hands everywhere.

SUMNER L. KOCH.

THE book by Wallace Marshall, *Essentials of Medical Research*[2] is all that the title implies as well as being a philosophic treatise on the ethics of medicine and medical research. The author discusses the reasons for carrying on medical research as well as the benefits and hardships which research might entail. Research requires a proper attitude of mind, perseverance, and basic honesty. Elaborate equipment is not always necessary; many problems can be solved by the researcher's five senses, a pad of paper, and a pencil. Where the investigator is not associated with a University and a well-equipped laboratory, Marshall gives hints as to how financial aid and equipment may be secured. The book is full of helpful, practical advice on collection and correlation of data, study of the literature, preparation of reports and graphs, photographs and statistics; and much valuable information on how to prepare a manuscript for publication and where to send it. It could be profitably read by any physician regardless of his research experience and could well be recommended to medical students and interns.

MICHAEL L. MASON.

[1] SURGERY OF REPAIR AS APPLIED TO HAND INJURIES. By B. K. Rank, M.S. (Melbourne), F.R.C.S. (England), F.R.A.C.S., and A. R. Wakefield, M.S. (Melbourne), F.R.C.S. (England), F.R.A.C.S. Foreword by Sir Gordon Gordon-Taylor. 256 pages, 188 illustrations. $8.00. Edinburgh, London: E. & S. Livingstone, Ltd., 1953.

[2] ESSENTIALS OF MEDICAL RESEARCH. By Wallace Marshall, M.D. 176 pages. $3.00. New York: Vantage Press, Inc., 1953.

THE small volume *Diagnosis of Acute Abdominal Pain*[1] is designed as an aid for the young physician confronted with an acute abdominal problem requiring not only correct diagnosis but a quick decision as to the efficacy of operation.

After discussing the various tests and methods of abdominal examination together with the diagnostic significance of the location and type of pain, the author reviews the problem of intestinal obstruction and the means of determining whether the obstruction lies in the small or the large intestine.

The second part of the book presents a large group of acute diseases arranged according to urgency of treatment, a classification which the author, based on his experience while a resident at Cook County Hospital, believed to be the most expedient approach. The acute abdominal pain of trauma is also considered, as is that occurring in infants, while the concluding chapter discusses the differential diagnosis of massive gastroesophageal hemorrhage.

The author includes a detailed review of the clinical manifestations of the diseases he describes, corroborating his discussion with a consideration of pathologic factors where these have an immediate bearing on the clinical picture. Illustrations are also used wherever possible to clarify the presentation.

While the author intended the book primarily for the intern, surgical resident, or young surgeon, so effectively has he classified and presented his material in this crucial area that this small reference book will be of value to any physician who must diagnose and decide how best to treat the emergency acute abdominal condition. ORVILLE F. GRIMES.

TECHNICAL knowledge and ability are only part of the attributes of a good surgeon. The attainment of surgical judgment, based on a comprehensive understanding of physiology, pathology, and anatomy, is of equal importance. *Nash's Surgical Physiology*,[2] second edition, as edited by Brian Blades and written by him and 11 of his associates in surgery at the George Washington School of Medicine, contributes greatly to this end.

The book covers the subject very well. Detail and experimental information have been largely omitted, and the contents of the volume, for the most part, are practical, making it of great value to the clinical surgeon and the student.

In recent years a large amount of physiologic data has accumulated which has influenced cardiovascular surgery, the postoperative care of the patients, the management of disturbances of electrolyte and fluid balance, surgery of the endocrine system, anesthesiology, and other fields related to surgery. *Nash's Physiology*, supplemented with current literature, is an excellent textbook for the student and an excellent reference book for the surgeon. OLIVER H. BEAHRS.

[1]DIAGNOSIS OF ACUTE ABDOMINAL PAIN. By William Requarth, M.D. Foreword by Warren H. Cole, M.D. 243 pages, 79 illustrations. $5.00. Chicago, Ill.: Year Book Publishers, Inc., 1953.

[2]NASH'S SURGICAL PHYSIOLOGY. Revised and edited by Brian Blades, M.D. 2nd rev. enl. ed. 686 pages, 35 illustrations. $12.50. Springfield, Ill.: Charles C Thomas, 1953.

IN considering the volume *Clinical Roentgenology*[3] the reviewer is impressed with the fact that a tremendous amount of work must have gone into the preparation. It is readily apparent that a large number of x-ray films must have been studied and sorted over in order to obtain the excellent selections which best exemplify the various diseased condition in which roentgenograms may be diagnostically helpful. From the point of view of the general surgeon, such as this reviewer, the selected photographs are very clear. The writers have adopted a very convincing and helpful expedient in labeling, by little over-printed arrows on the photographs, the various points that they wish to bring out. The written material is concise and to the point. It explains very well the selected photographs which it accompanies.

To obtain catholicity of opinion it was thought desirable by this reviewer, to have the point of view of a specialist in radiology. The radiologist at the hospital where the reviewer works studied this volume. He agreed that the films selected for photography and publication were well chosen and that they illustrated well the conditions which they purported to represent. He commented enthusiastically upon the completeness of the bibliography at the end of each of the sections. A comprehensive index has been carefully prepared. It was his opinion that this book constituted a valuable reference work. The radiologist and the reviewer both noticed that there was some wasted space and believed that the publishers might have economized in this respect. We both agreed that technically the publishers had done an excellent job in producing clear reproductions of radiographs on high grade paper and with excellent detail.

This reviewer and his radiologic associate recommend this book as a valuable reference volume for both specialists and general medical men.

MARTIN B. TINKER.

THE volume *Pictorial Introduction to Neurological Surgery*[4] has been written in an attempt to bring the surgical techniques employed by the senior author in his clinic to the general surgeon who may be required to care for the patient with a craniocerebral injury away from neurosurgical centers. This short, extremely well illustrated book may be of considerable interest to the American neurologic surgeon who may be interested in comparing the techniques employed in one of the clinics of England. The book is interestingly written and concerns itself almost entirely with neurosurgical techniques. It seems a pity that so much effort should have been expended to produce this book which deals with but a small facet in the care of craniocerebral injuries, insofar as

[3]CLINICAL ROENTGENOLOGY. Vol. 1.—DEVELOPMENTAL AND SYSTEMIC CONDITIONS AND LOCAL LESIONS IN THE EXTREMITIES. By Alfred A. de Lorimier, Henry G. Moehring, and John R. Hannah. 492 pages, illustrated. $18.50. Springfield, Ill.: Charles C Thomas, 1953.

[4]PICTORIAL INTRODUCTION TO NEUROLOGICAL SURGERY. By G. F. Rowbotham and D. P. Hammersley. 108 pages, 81 illustrations. $4.50. Baltimore: The Williams & Wilkins Co., 1953.

the greater number of these patients do not require surgery but instead, good nursing care which is even less available than the services of one who can open the skull, expose the brain, and stop intracranial bleeding. It would seem that there are very few who know how to position the unconscious patient in bed and maintain an adequate airway and nutrition.

Considerable emphasis is placed upon the anatomy of the scalp and the methods of preparing and closing scalp lacerations and flaps. There are excellent illustrations, perhaps the best I have ever seen, of the layers and blood vessels of the scalp, skull, and meninges and these serve to illustrate very well the sites of intracranial bleeding.

This book would be of considerable value to one who may have had little or no training in neurologic surgery or to the student who may wish to see illustrated some of the techniques which have been employed by the neurologic surgeon.

NICHOLAS WETZEL.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

PERIMETRY. By Joshua Zuckerman, B.SC., M.D., C.M., F.A.C.S. 391 pages, 156 illustrations. $10.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

A LA RECHERCHE D'UNE ETHIQUE MEDICALE. By Louis Portes. 212 pages. 800 fr. Paris: Masson & Cie; Presses Universitaires de France, 1954.

FRENCH'S INDEX OF DIFFERENTIAL DIAGNOSIS. Edited by Arthur H. Douthwaite, M.D., F.R.C.P. 7th ed. 1046 pages, 731 illustrations of which 200 are in color. Baltimore: The Williams & Wilkins Co., 1954.

TRANSACTIONS OF THE AMERICAN GOITER ASSOCIATION. 1953 Annual Session, May 7, 8, and 9, Drake Hotel, Chicago, Illinois. 423 pages, illustrated. $13.50. Springfield, Ill.: Charles C Thomas, 1954.

FUNDAMENTALS OF NEUROPATHOLOGY. By William Brooks Dublin, M.D. 685 pages, 329 illustrations. $18.50. Springfield, Ill.: Charles C Thomas, 1954.

PAMIĘTNIK ZJAZDU CHIRURGÓW DZIECIĘCYCH; W LUBLINIE—14 II 1953. By Prof. Dr. Med. Alojzy Maciejewski. 88 pages, illustrated. Warszawa: Panstwowy zaklad wydawnictw lekarskich, 1953.

SYMPOSIUM ON PROTEIN METABOLISM. Proceedings of the Nutrition Symposium held at the University of Toronto, Toronto, Ontario, Canada, October 30th, 1953. By A. E. Axelrod, J. R. Beaton, Paul R. Cannon, Bacon F. Chow, Laurence E. Frazier, Oliver H. Gaebler, Randolph H. Hughes, Ruth M. Leverton, Herbert Pollack, and J. Pruzansky. No. 8. 107 pages, illustrated. $1.50. New York: The National Vitamin Foundation, Inc., 1954.

ALTERN UND KRANKHEIT; GRUNDLAGEN EINER BIORHEUTISCHEN NOSOLOGIE. By Prof. Dr. med. Max Bürger. 2nd ed. 600 pages, 285 illustrations. DM 40. Leipzig: Veb Georg Thieme, 1954.

A HANDBOOK OF OPERATIVE SURGERY; SURGICAL UROLOGY. By R. H. Flocks, M.D., and David Culp, M.D. 392 pages, 118 illustrations. $9.75. Chicago: Year Book Publishers, Inc., 1954.

VETERANS ADMINISTRATION TECHNICAL BULLETINS; Series 10; Vol. 6, 1952 and 1953. 250 pages. Washington, D. C., 1954.

NEWER CONCEPTS OF THE CAUSES AND TREATMENT OF DIABETES MELLITUS. Proceedings of the Symposium on Diabetes Sponsored by the New York Diabetes Association and held at Memorial Hospital and the New York Academy of Sciences, New York City, October 8, 1953. 181 pages, illustrated. $2.50. New York: The National Vitamin Foundation, Inc., 1954.

SEVENTY-FIVE YEARS OF MEDICAL PROGRESS; 1878–1953. Edited by Louis H. Bauer, M.D., F.A.C.P. 286 pages. $4.00. Philadelphia: Lea & Febiger, 1954.

A SYNOPSIS OF ANESTHESIA. By J. Alfred Lee. 3rd ed. 483 pages, 72 illustrations. $3.50. Baltimore: The Williams & Watkins Co., 1953.

RESECTION-RECONSTRUCTION OF THE HIP; ARTHROPLASTY WITH AN ACRYLIC PROSTHESIS. By Jean Judet, Robert Judet, Jean Lagrange, and Jean Dunoyer. Edited by K. I. Nissen. 151 pages, 101 illustrations. $7.00. Edinburgh and London: E. & S. Livingstone, Ltd., 1954.

INSUFFLATION UTÉRO-TUBAIRE KYMOGRAPHIQUE; MÉTHODE POUR LE DIAGNOSTIC ET LE TRAITEMENT DE LA STÉRILITÉ TUBAIRE. By Louis Bonnet. 274 pages, 88 illustrations. 1.600 fr. Paris: Masson & Cie, 1954.

ANNUAL REVIEW OF MEDICINE. Edited by Windsor C. Cutting, and Henry W. Newman. Vol. 5. 490 pages, $7.00. Stanford, California: Annual Reviews, Inc., 1954.

A CURRICULUM FOR SCHOOLS OF MEDICAL TECHNOLOGY. Edited by Israel Davidsohn, M.D. Associate Editor, Kurt Stern, M.D. 3rd ed. 122 pages, illustrated. Muncie, Indiana: Registry of Medical Technologist of the American Society of Clinical Pathologists, 1954.

HYPERTENSION AND NEPHRITIS. By Arthur M. Fishberg, M.D. 5th enl. rev. ed. 986 pages, 49 illustrations. $12.50. Philadelphia: Lea & Febiger, 1954.

PRESERVATION AND TRANSPLANTATION OF NORMAL TISSUES. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S. Assisted by Joan Etherington. A Ciba Foundation Symposium. 236 pages, 55 illustrations. $6.00. Boston: Little, Brown & Co., 1954.

HISTOLOGY. Edited by Roy O. Greep, Ph.D., with 13 contributors. 953 pages, 648 illustrations. $15.00. New York: The Blakiston Co., Inc., 1954.

DER HERZKATHETERISMUS BEI ANGEBORENEN UND ERWORBENEN HERZFEHLERN. By Prof. Dr. O. Bayer, Dr. Fr. Loogen, and Dr. H. H. Wolter. With a foreword by Prof. Dr. E. Boden. 191 pages, 131 illustrations. $8.60. Stuttgart: Georg Thieme Verlag, 1954.

KINDERORTHOPAEDIE. By Rupprecht Bernbeck. Foreword by Prof. Dr. Georg Hohmann. 232 pages, 171 illustrations. $9.30. Stuttgart: Georg Thieme Verlag, 1954.

DOCTOR DAN; PIONEER IN AMERICAN SURGERY. By Helen Buckler. 381 pages, illustrated. $5.00. Boston: Little, Brown & Co., 1954.

CLINICAL ORTHOPAEDICS; SOFT-TISSUE CONDITIONS AROUND JOINTS. Anthony F. DePalma, Editor-in-Chief. With the assistance of the Associate Editors and the Board of Advisory Editors. No. 3. 230 pages, illustrated. $7.50. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

FRED W. RANKIN,* Lexington, Kentucky, *President*
ALFRED BLALOCK, Baltimore, *President-Elect*

PRELIMINARY PLANS FOR THE 40TH CLINICAL CONGRESS—CONVENTION HALL, ATLANTIC CITY, NEW JERSEY, NOVEMBER 15 TO 19, 1954

THE 40th Clinical Congress of the American College of Surgeons will be held in Atlantic City, November 15 through 19, 1954. This is the first Congress ever to be held in this famous resort city which is now celebrating its Centennial Year.

Headquarters for meetings and exhibits will be Convention Hall, the world's largest auditorium and meeting center, located on the famous Boardwalk. Atlantic City has ample hotel accommodations, and 31 hotels near the meeting hall have set aside sufficient rooms for Congress visitors.

This year's program of education has been expanded and carefully planned to meet contemporary needs. New features include the following: joint specialty sessions, of interest to more than one field; eight postgraduate courses, four in special fields of surgery; more forum papers, with an increased number in the specialties; more film symposia, including one on surgery of the head and neck, and one on spectacular lesions in surgery; new films on cardiovascular surgery, surgery of the intestines, surgery of the esophagus and stomach, surgery of the biliary tract and pancreas (for many of the motion pictures the authors will be present to give personal narrations); color television of operative clinics "imported" from Philadelphia, sixty miles away; greatly increased seating capacity for all programs; and finally, more scientific and technical exhibits.

ATLANTIC CITY ADVISORY COMMITTEE ON ARRANGEMENTS

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ELMER PETER WEIGEL, Plainfield

OFFICIAL MEETINGS

Only two official evening sessions will be held this year. At the opening evening meeting of the Clinical Congress, on Monday, Dr. C. H. deT. Shivers, Chairman of the Atlantic City Advisory Committee on Arrangements, will welcome visitors to the Congress. Dr. Evarts A. Graham, Chairman of the Board of Regents, will introduce guests. Robert H. Kennedy, New York, will give the Oration on Trauma. Alan Gregg, Vice President, The Rockefeller Foundation, New York, will give the Martin Memorial Lecture.

The Annual Meeting of Fellows will be held on Thursday afternoon. On Friday evening, the annual Convocation will be held. Initiates will be presented for Fellowship, honorary Fellowships

*Deceased, May 22, 1954.

conferred, and new officers inaugurated. Alfred Blalock, incoming president of the College, will give the Presidential Address.

Tuesday and Wednesday evenings will be left free for special group activities. On Thursday evening the Motion Picture Symposium will be held.

GENERAL SESSIONS

General scientific sessions will begin this year with a panel discussion on "Benign Lesions of the Lower Esophagus" at 10 a.m. Monday morning. At 3:30 p.m. another discussion, on "Diverticulitis" will be held. Subjects for succeeding days follow:

Tuesday, 1:30–3 p.m.—Hypothermia; 3:30–5 p.m.—Hormonal Balance in Surgery
Wednesday, 3:30–5 p.m.—Peripheral Arterial Disease
Thursday, 1:30–3 p.m.—The Use and Abuse of Antibiotics in Therapy

CLINICOPATHOLOGY CONFERENCES

Again this year two clinicopathology conferences have been scheduled, one on Monday at 1:30 p.m. and the second on Wednesday at the same time.

SPECIAL SYMPOSIA

The Symposium on Trauma will be held Tuesday afternoon, from 2 to 5 p.m. The Symposium on Cancer will be held Wednesday, at the same time. A symposium on Graduate Training in Surgery and the Surgical Specialties is scheduled, time to be announced. Several motion picture features are planned, including a Motion Picture Symposium on Thursday evening. In the otolaryngology program there will be two symposia: on Wednesday morning "Congenital Diseases of the Larynx," "Borderline Malignant Lesions of the Larynx," and "Carcinoma of the Mouth and Tongue, Including Hemihydidectomy in the Performance of the Commando Operation"; on Thursday morning "Nasopharyngeal Fibroma," "Cancer of the Nasopharynx," and "X-Ray Diagnosis of Lesions of the Nasopharynx."

POSTGRADUATE COURSES

Postgraduate courses have been increased to eight this year, in answer to requests for more of these highly valuable courses. Courses will be held mornings, Monday through Thursday, 8:30 through 11:30 a.m. Attendance will be limited, and open only to those who register in advance. Fee is $5.00 per course. Titles and chairmen follow:

Cardiovascular Surgery. JOHN H. GIBBON, JR., Chairman
Preoperative and Postoperative Care. JONATHAN E. RHOADS, Chairman
Surgery of the Lower Esophagus, Stomach, and Duodenum. REGINALD H. SMITHWICK, Chairman
Diseases of the Liver, Biliary Tract, and Pancreas. NATHAN A. WOMACK, Chairman
Combined Injuries to the Extremities. HARRISON L. MCLAUGHLIN, and HAROLD A. ZINTEL, Co-chairmen
Gynecology and Obstetrics. THADDEUS L. MONTGOMERY, Chairman
Surgical Aspects of Pulmonary Disease. RICHARD H. OVERHOLT, Chairman
Lower Extremity Amputations and Prostheses. HARRY D. MORRIS, Chairman

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

The Forum on Fundamental Surgical Problems has become an especially distinguished program, where younger surgeons have the opportunity to present reports of their research. More sessions are planned this year, morning and afternoon, Monday through Friday. An added feature this year will be the summary session on Friday, wherein investigative reports heard during the week will be reviewed. Presiding officers will emphasize and stress important developments of the year.

OTOLARYNGOLOGY SESSIONS

Separate sessions for otolaryngologists have also been expanded this year, to run three full days. For the first time in this specialty, films—with personal narration—will be part of the three morning programs. An outline in brief is presented in the following:

Tuesday, 9–12 noon—Motion Pictures with Personal Narration; 3:30–5 p.m.—Panel discussion on Relationship of Blood Dyscrasias to Otolaryngology, and The Control of Bleeding
Wednesday, 9–10:30 a.m.—Symposium on Congenital Diseases of the Larynx, Borderline Malignant Lesions of the Larynx, Carcinoma of the Mouth and Tongue Including Hemihyoidectomy in the Performance of the Commando Operation; 10:45–12 noon—Motion Pictures with Personal Narration; 3:30–5 p.m.—Panel discussion on Management of Sinus Disease
Thursday, 9–10:30 a.m.—Symposium on Nasopharyngeal Fibroma, Cancer of the Nasopharynx, X-Ray Diagnosis of Lesions of the Nasopharynx; 10:45–12 noon—Motion Pictures with Personal Narration

OPHTHALMOLOGY SESSIONS

Separate sessions for ophthalmologists will include panel discussions on three separate afternoons, and motion pictures with personal narration on three evenings. In brief, the program will run as follows:

Tuesday, 1–3 p.m.—Surgical Management of Diseases of the Cornea; 8–10 p.m.—Motion Pictures
Wednesday, 1–3 p.m.—Minor Surgical Problems of the Eye and Adnexae; 8–10 p.m.—Motion Pictures
Thursday, 1–5 p.m.—Selection of Operative Technique in Retinal Separation; 8–10 p.m.—Motion Pictures

UROLOGY

Increased sessions in this specialty have been planned for this year. The Advisory Council for Urology has scheduled four panel discussions and, for some of these sessions, the council has chosen subjects of common interest to men in other fields of surgery. These meetings will be conducted as joint sessions, with representatives from the other specialties participating.

Wednesday, 9–10:30 a.m.—The Clinical Management of Spinal Cord Injuries—Collaborators in Neurosurgery, Orthopedics; 10:45–12:15—Incontinence in Women—Collaborators in Gynecology, Pathology
Thursday, 9–10:30 a.m.—The Abdominal Mass—Collaborators in General Surgery, Gynecology, Pathology
Friday, 1:30–3 p.m.—Postoperative Depletion States of Urological Patients

GYNECOLOGY AND OBSTETRICS

Five important panel discussions in this specialty will be held from Wednesday through Friday:

Wednesday, 1:30–3 p.m.—Urological Injuries in Pelvic Surgery, Their Prevention and Treatment—Joint Specialty Session with Urologist; 3:30–5 p.m.—Differential Diagnosis and Treatment of Vaginal Discharges
Thursday, 1:30–3 p.m.—Perinatal Pathology
Friday, 1:30–3 p.m.—Review of Modern Diagnostic Tests of Pregnancy; 3:15–4:45 p.m.—Problems of Labor Related to the Myometrium

THORACIC SURGERY PANEL DISCUSSION SESSIONS

On Friday afternoon, from 1:30 to 4:45 p.m., two panel discussions will be held in this specialty: "Thoracic Surgery in the Aged," and "New Developments in the Surgery of Heart Disease."

NEUROLOGIC SURGERY PANEL DISCUSSION SESSIONS

On Thursday afternoon, from 1:30 to 3 p.m., "Experience in the Treatment of Intracranial Meningiomas" will be discussed. On Friday, at the same time, "Electrolyte Balance and Postoperative Infections in the Neurosurgical Patient" will be presented.

PLASTIC SURGERY PANEL DISCUSSIONS

Two important topics will be discussed on Friday afternoon, from 1:30 to 4:45 p.m., "Problems in Cleft Lip and Cleft Palate Repair" and "Reconstructive Surgery of the Nose."

MOTION PICTURES, CINÉ CLINICS, AND TELEVISION

Ciné clinic films will show operative techniques in the southern and midwestern states and Canada. Color television, under the chairmanship of Dr. I. S. Ravdin, will be imported from Philadelphia, sixty miles away. Dr. Hilger Perry Jenkins, Chairman of the Motion Pictures Committee, announces several outstanding new motion pictures, including "Surgery of the Head and Neck," "Spectacular Lesions in Surgery," and new films on cardiovascular surgery, surgery of the intestines, esophagus and stomach, and surgery of the biliary tract and pancreas. Personal narration will accompany the films. The otolaryngology sessions will also present new films.

Anyone wishing to contribute medical motion pictures to the Congress film program should forward these pictures for immediate review and approval by the Committee to Dr. H. Prather Saunders, Secretary, Committee on Medical Motion Pictures, 40 East Erie Street, Chicago 11, Illinois.

ADVANCE REGISTRATION

Official registration forms for advance registration, postgraduate courses, and transportation are now available and may be obtained from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois. Early registration insures more desirable hotel and transportation accommodations, and better assurance of acceptance in the postgraduate course of your choice.

No registration fee is charged Fellows whose dues are paid through December 31, 1953; no registration fee is required of Initiates, Junior Candidates, or Surgical Residents whose applications are accompanied by a letter of identification from the hospital administrator or chief of surgery. Non-Fellows will be charged $20.00 and members of the Federal Services $10.00.

HOTEL RESERVATIONS

Official forms for hotel reservations must be obtained from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois. To insure obtaining the accommodations you wish hotel reservations should be made in advance.

SCIENTIFIC AND TECHNICAL EXHIBITS

More exhibit booth space will be available this year than ever before. Forms to be used in applying for scientific exhibit space may be obtained from Dr. Robert S. Myers, Chairman, Committee on Scientific Exhibits. Deadline for requests for exhibit space is August 31. Technical exhibits are under the direction of James S. Shannon, General Manager, SURGERY, GYNECOLOGY AND OBSTETRICS.